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ABSTRACT

This book contains 16 papers from the 1974 conference held by the Pregnancy and Infancy Branch of the National Institute of Child Health and Human Development to: (1) assess the photobiological processes involved in phototherapy used in treatment of neonatal hyperbilirubinemia, and (2) to document long term clinical experience with the treatment in all parts of the world. The conference focused on long term implications regarding the safety of the treatment. Papers fall under one of three headings: Long Term Clinical Experience; Pathobiology: Basic and Clinical Considerations; and Physical Science Approaches to Problems of Phototherapy. Also included are the transcripts of conference discussions on various related topics. (SB)

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PHOTOTHERAPY FOR NEONATAL HYPERBILIRUBINEMIA

LONG-TERM IMPLICATIONS

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Phototherapy for Neonatal Hyperbilirubinemia

Long-Term Implications

Editors

Audrey K. Brown, M.D.
Department of Pediatrics
State University of
New York, Downstate
Medical Center

Jane Showacre, Ph.D.
Pregnancy and Infancy
Branch
National Institute of Child Health
and Human Development

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Foreword

Since phototherapy was introduced in the 1950's it has been used in reducing serum bilirubin levels in the newborn infant with hyperbilirubinemia. Currently, the therapy, in various modifications, is widely used in hospitals throughout the Nation. Research has focused largely on serum bilirubin and short-term effects of the treatment. A number of unresolved questions remain about the physiologic mechanisms invoked by light and the sequelae to phototherapy, both acute and long-term in the human infant. The National Institute of Child Health and Human Development has sought to further stimulate the interest of investigators in these questions. This conference, convened April 24–26, 1974, at the National Institutes of Health, Bethesda, Md., is part of the effort. The contributions of diverse fields to the problem are evident in the presentations of the distinguished clinical and basic scientists who attended. It is our hope that these proceedings will further the concerted studies of the pediatrician, biochemist, physicist, and photobiologist and bring us closer to an optimal treatment of jaundice in the newborn.

EILEEN G. HASSELMEYER, Ph.D.
Program Director
Pregnancy and Infancy Branch
National Institute of Child Health and Human Development

Preface

Hyperbilirubinemia of the neonate and the attendant risk of kernicterus remains a major problem in nurseries throughout the world. In recent years there has been growing appreciation of the risk of development of bilirubin encephalopathy at relatively low levels of bilirubin in infants who have associated clinical factors that augment the potential for development of kernicterus, such as hypoxia, acidosis, hypoproteinemia, and hemolysis. Estimates of the number of infants at actual risk of kernicterus are difficult to arrive at, but it is known that about 17 percent of white infants weighing less than 2,500 grams at birth develop serum bilirubin levels in excess of 15 milligrams percent, while 9 percent of black infants of the same weight develop hyperbilirubinemia of this degree. Further, about 3 percent of full-term infants weighing more than 2,500 grams are likely to have serum bilirubin levels in this range, both in the black and the white populations. It has also recently been appreciated that among Mexican Americans and Chinese populations there may be exaggeration of hyperbilirubinemia as compared with black and white populations.

This degree of hyperbilirubinemia has been associated with significant alterations in motor development, and in many instances, particularly in those small infants at greatest risk, bilirubin encephalopathy can, and does, occur at serum bilirubin levels less than 15 milligrams percent. Because the specific risk to an individual infant, at any degree of hyperbilirubinemia, is difficult to assess clinically, there has been a growing tendency to prevent it altogether or to limit its degree. Because of this tendency, the advent of phototherapy for hyperbilirubinemia has been widely accepted as both simple and effective, and only recently has there been appreciation that phototherapy is indeed a "pharmaceutical" agent that should be appraised both for its immediate safety and efficacy and for its possible long-term implications.

Photobiological data from other species indicate that light can be both beneficial and detrimental to many biological processes. The time has come to evaluate the risk-benefit ratio of this modality of therapy for hyperbilirubinemia of the neonate.

There has been little, thus far, to indicate immediate hazards from this form of therapy, but long-term sequelae have not been adequately assessed. A review of the experience of the past 15–17 years with this agent was thought to be useful. In April 1974, the Pregnancy and Infancy Branch of the National Institute of Child Health and Human Development sponsored a conference to assess the photobiological processes involved in phototherapy, as well as to document the long-term clinical experience of clinicians from all parts of the world who have used light in the treatment of hyperbilirubinemia since 1958.

The papers and discussions presented in this book by distinguished investigators from the clinical and basic sciences illustrate not only the breadth of the problem, but also the value of an interdisciplinary approach to its resolution.

We thank the participants, as well as our fellow moderators, Dr. Richard Behrman, Dr. Rudi Schmid, and Dr. Jerold Lucey, for their direct contributions to this volume.

AUDREY K. BROWN, M.D.
State University of
New York
Downstate Medical Center

JANE SHOWACRE, Ph.D.
Pregnancy and
Infancy Branch
National Institute of Child Health
and Human Development

Participants

Duane Alexander, M.D.
Special Assistant to the Scientific Director
National Institute of Child Health and Human Development
Bethesda, Maryland

Robert J. Anderson, Ph.D.
Senior Scientist
Corporate Research Department
Beckman Instruments, Inc.
Fullerton, California

David W. Bailey, M.D.
Chief, Pediatric Service
National Naval Medical Center
Bethesda, Maryland

Richard E. Behrman, M.D.
Professor and Chairman, Department of Pediatrics
College of Physicians and Surgeons
Columbia University
New York, New York

Paul D. Berk, M.D.
Chief, Section on Diseases of the Liver
Digestive Diseases Branch
National Institute of Arthritis, Metabolism, and Digestive Diseases
Bethesda, Maryland

David R. Bickers, M.D.
Assistant Professor
Department of Dermatology
College of Physicians and Surgeons
Columbia University
New York, New York

Audrey K. Brown, M.D.
Professor, Department of Pediatrics
State University of New York
Downstate Medical Center
Brooklyn, New York

Richard A. Cahill, M.D.
Chief, Pediatric Hematology
National Naval Medical Center
Bethesda, Maryland

Friedrich Karl Friederiszick, M.D.
Direktor der stadtischen Kinderklinik
Krankenstalten Dortmund
Professor, Department of Pediatrics
University of Munster-Westfalia
Dortmund, Germany

Lawrence M. Gartner, M.D.
Associate Professor, Department of Pediatrics
Director, Division of Neonatology
Albert Einstein College of Medicine
Bronx, New York

Leonard C. Harber, M.D.
Professor and Chairman, Department of Dermatology
College of Physicians and Surgeons
Columbia University
New York, New York

Eileen G. Hasselmeyer, R.N., Ph.D.
Program Director, Pregnancy and Infancy Branch
National Institute of Child Health and Human Development
Bethesda, Maryland

J. Woodland Hastings, Ph.D.
Professor, Department of Biology
Harvard University
Cambridge, Massachusetts

Jean Hewitt
Research Associate, College of Medicine
University of Vermont
Burlington, Vermont

Joan E. Hodgman, M.D.
Professor, Department of Pediatrics
Director, Newborn Service
Los Angeles County-University of Southern California Medical Center
Los Angeles, California

Leonard Indyk, Ph.D.
Assistant Professor, Department of Pediatrics
College of Physicians and Surgeons
Columbia University
New York, New York

Barbara Jackson
Biologist, Program Statistics and Analysis Branch
National Institute of Child Health and Human Development
Bethesda, Maryland

L. Stanley James, M.D.
Professor, Department of Pediatrics
College of Physicians and Surgeons
Columbia University
New York, New York

John D. Johnson, M.D.
Assistant Professor, Department of Pediatrics
Stanford University Medical Center
Stanford, California

Lois Johnson, M.D.
Associate Pediatrician, Neonatal Research Section on New Born Pediatrics
Pennsylvania Hospital
University of Pennsylvania
Philadelphia, Pennsylvania

Jaime Kapitulnik, Ph.D.
Research Biochemist, Metabolic Laboratory
Hadassah University Hospital
Jerusalem, Israel

Cyril D. Karabus, M.D., M.R.C.P., F.R.C.P.E.
Senior Lecturer and Pediatrician-Hematologist
Department of Pediatrics
University of Cape Town
Rondebosch, Cape Province
South Africa

Norman Kretchmer, M.D.
Harold K. Faber Professor of Pediatrics
Stanford University
Consultant, National Institute of Child Health and Human Development
Bethesda, Maryland

Emanuel Landau, Ph.D.
Chief, Epidemiologic Studies Branch
Division of Biological Effects
Bureau of Radiological Health
Food and Drug Administration
Rockville, Maryland

Richard D. Landes, M.D.
Chief, Newborn Service
Walter Reed Medical Center
Silver Spring, Maryland

Charles U. Lowe, M.D.
Scientific Director
National Institute of Child Health and Human Development
Bethesda, Maryland

Jerold F. Lucey, M.D.
Professor, Department of Pediatrics
College of Medicine
University of Vermont
Burlington, Vermont

Antony F. McDonagh, Ph.D.
Assistant Professor, Department of Pharmaceutical Chemistry
University of California
San Francisco, California

T. Allen Merritt, M.D.
Pediatric Medical Officer, Pregnancy and Infancy Branch
National Institute of Child Health and Human Development
Bethesda, Maryland

Robert W. Miller, M.D.
Chief, Epidemiology Branch
National Cancer Institute
Bethesda, Maryland

José Obes-Polleri, M.D.
Director, Newborn and Premature Center
Ministry of Public Health
Montevideo, Uruguay

Gerald B. Odell, M.D.
Professor, Department of Pediatrics
School of Medicine
Johns Hopkins University
Baltimore, Maryland

Jiro Ogawa, M.D.
Professor and Chairman, Department of Pediatrics
Nagoya City University
Nagoya, Japan

Yunosuke Ogawa, M.D.
Professor, Department of Pediatrics
Nagoya City University
Nagoya, Japan

J. Donald Ostrow, M.D.
Medical Investigator, Veterans Administration
Associate Professor, Department of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Paul H. Plotz, Ph.D.
Senior Investigator
Arthritis and Rheumatism Branch
National Institute of Arthritis, Metabolism, and Digestive Diseases
Bethesda, Maryland

Jean-Pierre Ploussard, M.D.
Assistant Chef de Clinique
Hospital Bretonneau
University Paris VII
Paris, France

Rudi Schmid, M.D., Ph.D.
Professor, Department of Medicine
University of California
San Francisco, California

Jane Showacre, Ph.D.
Health Scientist Administrator, Pregnancy and Infancy Branch
National Institute of Child Health and Human Development
Bethesda, Maryland

Calvin C. J. Sia, M.D.
Pediatrician
Childrens Medical Clinic
Honolulu, Hawaii

Kim-Leong Tan, M.B., M.R.C.P.E., D.C.H.
Senior Lecturer, Department of Pediatrics
Faculty of Medicine
University of Singapore
Singapore

Thomas P. Vogl, Ph.D.
Adjunct Professor, Radiation Physics
Department of Radiology
College of Physicians and Surgeons
Columbia University
New York, New York

Wolf W. Zuelzer, M.D.
Director, Children's Research Center
Children's Hospital of Michigan
Detroit, Michigan

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Purpose of the Conference

Audrey K. Brown

Since 1958, when Cremer first described the effect of light on serum bilirubin levels in newborn infants, phototherapy has been widely employed both to prevent neonatal hyperbilirubinemia as well as to control it.

Recognizing the widespread use of phototherapy in nurseries, staff of the National Institute of Child Health and Human Development (NICHD) in 1972 discussed with members of the Perinatal Biology and Infant Mortality Research and Training Committee means by which the NICHD might seek and offer support for solutions to questions arising in the use of phototherapy to control and treat hyperbilirubinemia in the neonatal period. The conference reported in this book is a direct outgrowth of a recommendation from that Committee that an international interdisciplinary conference be organized at which physicians and other scientists, long active in the field of phototherapy or photobiology, would be asked to share their experiences. It was hoped that through this means insight would be gained into the questions arising concerning long-term implications regarding safety. It was recognized that the data available would be based, in most instances, on the use of phototherapy without accurate information concerning the dose of irradiance. Nevertheless, the Committee felt that this large body of experiential data should not be lost.

The recent conferences organized by the National Academy of Sciences in Washington (February 1973) and by the National Foundation in Jerusalem (March 1974) did not attempt to include this particular body of clinical data, which would of necessity also encompass some anecdotal information. Further, it was felt that a vast new body of information was emerging concerning light biology and light physics that ought to be shared further with the medical community that was applying light therapy to infants.

In preparation for this conference, the NICHD sought to identify long-term studies of phototherapy that might have been performed anywhere in the world since the introduction of this modality to treatment for neonatal hyperbilirubinemia in 1958. We endeavored to include in this conference the majority of long-term studies in which the experimental design offers insight into any potentially detrimental effects of phototherapy.

Physicians with such long-term studies of infants receiving phototherapy were given several months in which to organize data in response to specific questions concerning the effects of light. In the efforts to identify studies relating to long-term studies, we gratefully acknowledge the assistance of F. Alison, M.D.; Lenore Ballowitz, M.D.; Johan Gentz, M.D.; Wong Hock Boon, M.D.; H. Cardin, M.D.; E. Croso, M.D.; Pamela A. Davies, M.D.; John A. Davis, M.D.; Peter M. Dunn, M.D.; Mario Ferreiro, M.D.; Peter Franke, M.D.; F. K. Friederiszick, M.D.; Eduardo Jurado Garcia, M.D.; H. De V. Hesse, M.D.; C.D. Karabus, M.D.; Jesus Linares, M.D.; José Obes-Polleri, M.D.; Jiro Ogawa, M.D.; S. Onishi, M.D.; Marcello Orzalesi, M.D.; H. D. Petermann, M.D.; Antonio Priolisi, M.D.; F. F. Rubaltelli, M.D.; José Senna, M.D.; K. L. Tan, M.D.; and T. Valaes, M.D.

In 1973 the NICHD appointed an ad-hoc advisory committee on phototherapy composed of pediatricians and others engaged in research in the field. This committee was charged to advise on the need for additional research and to consider experimental protocols designed to meet these needs. A series of meetings followed and led to the issuance of a request for proposals and the support by contract of current studies that seek to answer a number of questions regarding the safety of phototherapy in the treatment of neonatal hyperbilirubinemia.

From the investigations of these committees and from the work of the National Academy of Sciences Committee on Phototherapy in the Newborn, the following was evident:

1. Surprisingly few prospective studies of the safety of phototherapy have been performed, probably because its safety was assumed and there was little clinical appreciation that light might be detrimental.
2. Most studies to date have evaluated the efficacy of phototherapy in preventing hyperbilirubinemia of the premature. Followup was usually confined to the neonatal period. Relatively few studies have analyzed the use of phototherapy to control, rather than prevent, hyperbilirubinemia, and thus far have given insufficient basis for the development of guidelines for the use of light to control already established hyperbilirubinemia, which is of course, its most common use in practice today.
3. Surprisingly, no major studies of phototherapy could be identified concerning the reduction in the incidence of kernicterus through the use of phototherapy.
4. With regard to basic questions concerning the mechanism of action of light, while major advances had been made with regard to our understanding of how light affects bilirubin in vitro, no definite answer was available concerning its major mode of action in vivo.
5. With regard to the minimum "dose" required in vivo to promote most effective clearance of bilirubin, no data were available because in no study was the actual "dose" of light recorded.

Therefore, the conference was devoted to two aspects of phototherapy. The first sessions served the initial purpose of sharing experiences gleaned from the followup studies of infants who received phototherapy several years ago. For this experience we turned to our colleagues from other continents who have employed phototherapy for many years.

The second day considered areas that were largely overlooked in the early years of the use of light, namely, the chemical, physical, and biologic aspects of the interaction of light and man.

At the conclusion of the conference we addressed specific research needs in relation to the safety and efficacy of phototherapy and the problems of neonatal hyperbilirubinemia.

Pharmaceutical Photons

J. W. Hastings

When discussing phototherapy the following question often arises: Does light—to which we are all exposed all of our lives—really penetrate the body? Anyone who has looked carefully knows very well that it does, and one of the nicest ways to visualize this is to look at the painting of the 17th century French artist Georges de la Tour (figure 1). The newborn is certainly more transparent than the virgin.

Indeed if light does have a beneficial effect in phototherapy, it must

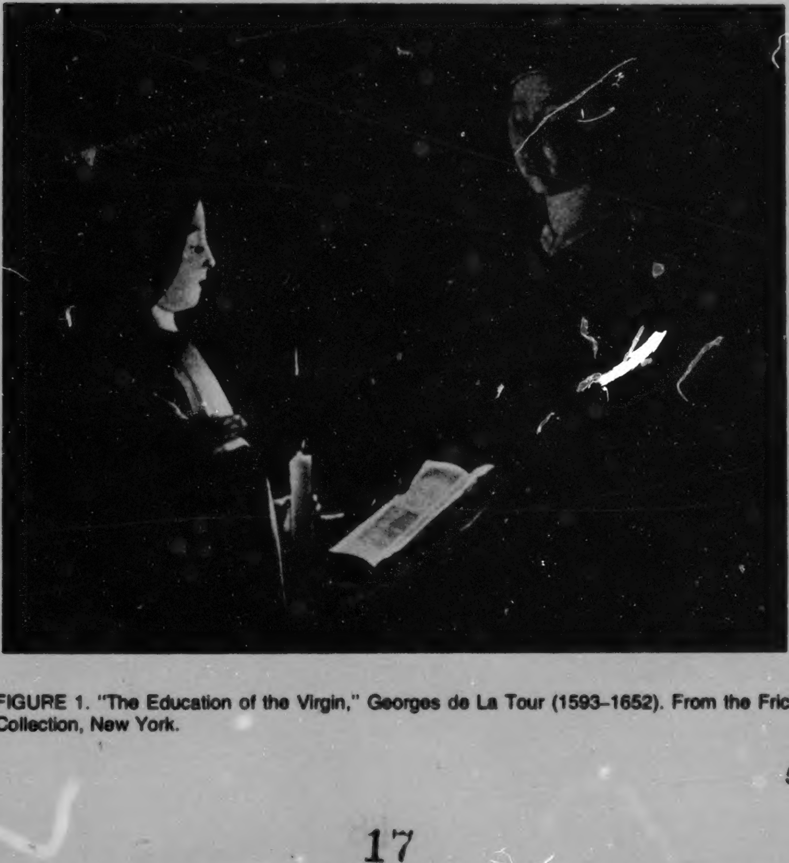

FIGURE 1. "The Education of the Virgin," Georges de La Tour (1593–1652). From the Frick Collection, New York.

penetrate, and the fundamental fact is that this light initiates photochemistry.

Gaining knowledge about the photochemical reaction or reactions is the central matter of concern, and it is precisely this challenge that has drawn the attention of so many of us outside of medicine. For as soon as the photon interacts with a molecule, a new chemistry comes into play. A potential drug action is thereby created in situ, wherever it may be that the photon is absorbed. The positive power and potential of such a technique is obviously enormous. in many respects. One can turn the "drug" on and off, administer it at widely different rates—in fact this represents the timed-release drug par excellence. One can build in specificity both chemically and in terms of physical location. Specific wavelengths of light can be aimed at specific chemical targets, excluding others.

But as with all drugs, light should be accorded appropriate respect. The photon that initiates a helpful reaction can equally well initiate a harmful reaction.

Obviously one reason for this special respect in the case of light is that our basic knowledge of photochemistry is still inadequate. I am not talking about applied photochemistry or about working out the messy details of the photochemistry of the cell, with its diverse substances, membranes, and interactions. The photochemistry of the cell is also an unknown, and we will undoubtedly have to get to work on this problem even without a good knowledge of the basic molecular photochemistry. What I refer to is the need for basic knowledge in the field.

Another reason for special caution in using phototherapy is the fact that because we live in light, we tend to think that we need not consider it as hazardous. This clearly is not the case. Pigmentation and other mechanisms to protect against light are abundant in living organisms. Even trees and plants, while they have elegant systems to capture the energy of the photon to fix carbon and thereby provide the nutritional basis for all life, are at the same time provided with protection against the light—they are in effect waging a constant battle against the concurrent destructive effects of light.

The idea that something could have both good and ill effects is not really foreign to us; certain substances, such as trace metals for example, are nutrients at a low concentration but may be toxic at higher levels. The example of oxygen as a toxic substance, while being essential to life, is well known in medicine. Life is believed to have had its origin and early evolution in an oxygen-free atmosphere. With the appearance of oxygen, new and energetically significant biochemical pathways involving oxygen evolved in the organism. But destructive oxidizing species were inevitably produced from the molecular oxygen, and biochemical systems that function to detoxify these occur in all aerobic forms. Catalase and peroxidase destroy H_2O_2. Just recently (1969) it has been shown that *erythrocuprein*, known for some 30 years as a blue cupro protein from the erythrocyte but having no assigned activity or function, is in fact an enzyme—now called superoxide dismutase—which breaks down the highly destructive oxidizing species superoxide ion, a reactive free radical form of oxygen that is ubiquitous in aerobic forms of life. Present evidence indicates that the toxicity of oxygen for anaerobes is explained by the fact that they lack this enzyme. Clearly the toxic effect of high oxygen in some aerobic systems may be explained by the inadequacy of the detoxification systems.

In any event, the conclusion is not unexpected or difficult to accept. The newborn is certainly relatively transparent, and since light can clearly initiate destructive photochemistry, caution with phototherapy seems altogether reasonable.

Let us discuss the nature of this destructive photochemistry. When a photon is absorbed by a molecule, the energy of the photon is transferred to the molecule, creating an electronically different form of the molecule, an excited state

$$D + h\nu \rightarrow D^*$$

where D is a dye, hν is photon and D^* is the higher energy electronically excited state of D. The energy involved is considerable. In the blue, a mole of photons, that is 6×10^{23} photons or one einstein, is equivalent to about 60 kilocalories (kcal). When we realize that the hydrolysis of ATP to ADP releases about 7 to 10 kcal, we see that photochemical reactions are about an order of magnitude more energetic.

The excited state D^* may have any one of several possible fates. It may lose the energy as heat and return to its original state.

$$D^* \rightarrow D + \text{heat}$$

It may lose the energy as a photon. This is fluorescence (F) if it occurs from the singlet or, if the excited state falls to a lower (triplet) energy level before emitting, phosphorescence (P)

$$^1D^* \rightarrow D + h\nu\ (F)$$
$$^1D^* \rightarrow {}^3D^* \rightarrow D + h\nu\ (P)$$

Finally the energy may be conserved or used to drive a chemical reaction. In general, related to its lifetime, this involves the triplet state.

$$^3D^* + A \rightarrow {}^1D + B$$

Note that in general the "chemical" status of the system remains essentially unaltered in the first two cases following the passage of a photon. Not so in the last case, since substance A has been converted to B. Or, for example, in photophosphorylation, light can drive the formation of ATP, an energy-requiring reaction. In other cases, a different kind of reaction might occur. In fact many different kinds of specific mechanisms are known, including ones in which energy transfer occurs from $^3D^*$ to still another molecule before the chemical changes occur.

In the oxidation of bilirubin, such an energy transfer does occur. The photooxidation is effected by a special high-energy form of oxygen, "active oxygen," actually an electronically excited species of oxygen that gets excited by energy transfer from the triplet excited dye. This active oxygen then oxidizes bilirubin (*B*).

$$\begin{aligned} {}^3D^* + {}^3O_2 &\rightarrow {}^1D + {}^1O_2^* \\ {}^1O_2^* + B &\rightarrow BO_2 \end{aligned}$$

This is an unusual type of oxygen whose existence and true identity have been recognized only in the last few years.

Actually, in both biological and chemical systems, the destructive effect of light in the presence of dye and oxygen—termed photodynamic action—has been known since the work of Raab in 1900. The most incisive, but long ignored studies were those of Kautsky in the 1930's. From a long series of experiments, he concluded that light energy absorbed by sensitizing dyes was transferred to oxygen according to the above equation, and that it was this species that was destructive.

A mechanism of this type was indicated first because direct energy transfer from the sensitizing dye to the substrate had to be ruled out on theoretical grounds; with some effective dyes, the energy is insufficient to transfer to substrate. Even in the apparently simpler case where substrate acts as its own sensitizer, which is probably the case with bilirubin, it was shown that the quantum yield increases with the concentration of substrate. Thus, in this case, a direct reaction between the excited state of the substrate and oxygen must be ruled out; a second molecule of substrate must participate.

But the most definitive experiment was Kautsky's elegant demonstration that the dye and substrate could be bound to physically separate grains of silica gel; only gaseous oxygen could come in contact with one and then diffuse and come in contact with the second. In view of his striking experiments, the fact that the Kautsky mechanism was disregarded for some 25 years in favor of an unstable sensitizer complex is difficult to understand.

The "rediscovery" of active oxygen followed Seliger's observation in 1960 that a red luminescent flash occurs upon mixing hydrogen peroxide (H_2O_2) and chlorox ($HClO$). Khan and Kasha attributed this luminescence to a metastable excited singlet oxygen molecule and recalled and reviewed the Kautsky experiments. The luminescence of excited oxygen is also unusual and has been shown to emit at a wavelength not predicted by theory. The excited state has an energy of about 22 kcal and should emit at about 1,270 nanometers (nm); actually it emits in the red at exactly twice that energy (635 nm). The explanation, which was not readily accepted, is that two excited states cooperate in the emission of one photon. In fact, the light emission of Northern Lights is attributed to such transitions.

So excited oxygen can be formed photochemically by energy transfer from an excited dye, or chemically by reaction of peroxide and chlorox, or even by electric discharge. In the presence of a substrate, whatever it may be, characteristic oxidation occurs under any of these conditions, and diagnostically so.

Thus it now appears that photodynamic action, as discovered by Raab in 1900, does in fact involve excited singlet oxygen. Raab showed for example that *Paramecium* could be readily killed by light at moderate levels in the presence of a small amount of a dye such as eosin or rose bengal, and that oxygen is absolutely required. No two had any deleterious effect in the absence of the third. Over the years it was found that there were many different dyes that were effective as sensitizers, and that almost anything biological suffers damage or killing—from viruses, bacteria, and mammals to pure proteins, enzymes, and nucleic acids. In time, various diseases caused by photodynamic action were elucidated, especially in domestic animals where the sensitizing dyes were by chance ingested in the diet. In his book on the subject in 1941, Harold Blum describes a region in Italy where there are flocks of only black sheep; a sensitizer occurs in the local plants and on ingestion is such that a white sheep would be killed by the light. So the black sheep finally has a more rational explanation!

What about plants, basking in bright sunlight with their green antennae? As shown experimentally, chlorophyll is an excellent sensitizer for photodynamic action. It turns out that carotenoids, those ubiquitous yellow pigments, protect plants. They react preferentially with excited oxygen dissipating its energy to heat. The "protective" nature of carotenoids had been known for some 10 years from the work of Stanier and colleagues, but not understood until 1969 when Foote showed that it has the general function of quenching excited oxygen. Carotenoids are now used clinically to treat patients who have a hypersensitivity to light. Individuals who previously were unable to remain in sunlight—or even daylight—can now live virtually normal lives simply by adding a beta carotene supplement to the diet.

I think that this excursion into the background of our knowledge of excited oxygen illustrates well the interdependence of, and crossfeeding between, basic and medical sciences. Ten years ago medical science could simply not have made any informed attempt to evaluate phototherapy in terms of the basic photochemical and physiological sequellae. Today that is clearly possible.

Secondly, I think we should allow ourselves to be truly impressed by the fact that the same agent can have both good and bad effects. In the case of phototherapy, reducing the total amount of light yet producing the same effect would seem to be desirable. Adding exogenous photosensitizers is a possibility but a very dangerous one, and extensive research would be required before it can be evaluated. In fact one of the real concerns in phototherapy is that drugs administered to either mother or infant may act as photosensitizers. There are cases where this has happened and caused catastrophic effects.

Another idea for improving effectiveness and decreasing potential for damage comes from our knowledge of photosynthesis. It has been known since the turn of the century that continuous light is not needed to keep photosynthesis going at maximum rate. Dark periods of up to 0.02 second (sec) cause no decrease in photosynthetic rate, and a flash of 1/1000 sec or more is all you need in between dark periods. This of course is simply explained by the fact that the primary absorption of light is always fast, while steps that follow—often called dark steps—are usually relatively slow. If one short flash of light can populate all of the absorbing elements in the system (*D* in our equations above), as it can, then no more light is really needed or usable until these *D* species are finished with this chemistry. Since the lifetime of triplet states is generally long, seconds or some fraction thereof, this seems to be potentially applicable to phototherapy. Experimentally, this question can be asked for bilirubin destruction, and if a similar result is found, the total amount of light exposure can be decreased. But, of course, perhaps the damaging action of light is also equally effective in intermittent light. Only research will lead us to the answers and the directions to take.

The only thing that we can be reasonably sure of is that more of a good thing is not necessarily better. This phenomenon is illustrated by a legendary account of the U.S. aid program for the Russian farmer after World War I, when they were given incubators for chicken eggs and instructed on how to use the instrument as a substitute for the setting hen. Set the incubator at 98° and wait for 3 weeks. The peasants decided to turn up the temperature, and they had hard boiled eggs in a much shorter time.

Long-Term Clinical Experience

Phototherapy: A Clinical Experience

Growth Retardation: A Reversible Side Effect?

Jean-Pierre Ploussard and Jean Colin

In 1958, Cremer, Perryman, and Richards[1] demonstrated that exposure of jaundiced babies to sunlight or artificial blue light decreased their plasma bilirubin levels, thus establishing phototherapy as a treatment for neonatal jaundice.

It has since been used widely in a number of countries, particularly South America,[2] England,[3] Italy, France,[4,5] and the United States,[6-11] with a high degree of effectiveness and causing no apparent noxious effects. Criticism concerning the unknown nature and possible toxicity of bilirubin photocatabolites has been raised, however, questioning the more or less long-term consequences of phototherapy.

The Premature Center of the Institute of Puericulture in Paris, directed by Professor Alison from 1957 until 1968, and subsequently by Professor Satge, introduced phototherapy in 1963 and has had extensive experience with this technique.

The first trials, on about 10 percent of the newborns weighing less than 2,000 grams admitted to the center, had shown the effectiveness of using light to lower plasma bilirubin as well as the apparent safety, so application was expanded in 1966. The preliminary results were reported in 1966,[4] and in 1969, a 6-year study of phototherapy was published.[5]

The present report deals with our clinical experience with phototherapy at the Premature Center from 1966 to 1972.

After studies appeared demonstrating the possible consequences of light exposure on growth in animals[12] and in premature babies,[9,11,13,14] we conducted a retrospective study of these factors, included herein.

CONDITIONS FOR PHOTOTHERAPY APPLICATION

The Premature Center is not directly affiliated with any one maternity clinic or hospital. Infants are referred from many hospitals and maternity clinics within the Paris area, with the principal criterion for admission being, until recently, a birth weight of less than 2,500 g. From 1966 to 1972, 4,787 newborns were admitted to the Center, of which 3,098 were treated for jaundice by phototherapy (neonatal hemolytic disease excluded). The number of infants admitted and percentage treated for each period are shown in table 1.

TABLE 1. *Percentage of newborns referred to the Premature Center submitted to phototherapy*

Years	No. of admissions	No. of light treated	Percent
1966–67	1,269	472	37
1968	640	510	78
1969–70	1,432	1,046	73
1971–72	1,446	1,070	74
Total	4,787	3,098	64

Selection for light therapy was made solely on the availability of a treatment unit once phototherapy was indicated: lottery or other arbitrary forms of selection were not used.

Philips phototherapy units were used in all cases from 1963 to 1971; blue light was provided by eight Philips fluorescent tubes (18 powder, 40 watts, 1.20 meters in length, maximum intensity between 4,600 to 4,800 angstrom (Å). After 1971, blue light was replaced by cool white light (White Industry bulbs, maximum intensity between 4,600 and 5,000 Å).

Up until 1967, discontinuous treatment was used, with therapy broken off every 6 hours for 2 hours. In 1967, continuous therapy was initiated. Infants were placed unclothed in the incubators, with gauze bandages protecting their eyes from the light. Incubator temperature was modified to take into account the heat given off by the lamps.

Regardless of the type of illumination, hyperbilirubinemia was the principal criterion for placing an infant under treatment. In otherwise healthy newborns, plasma bilirubin levels above 8 milligrams (mg)/100 milliliter (ml) on the second day and 10 mg/100 ml the third day were indicative of when treatment was to start. When factors such as low birth weight, hypoxia, acidosis, hypoglycemia, sepsis, or subcutaneous hematomae were present, however, treatment was begun for bilirubin levels below these figures.

The treatment period is from 4 to 6 days, depending on the decrease of the bilirubinemia. Each infant received between 70 and 95 foot-candles of light as measured by a lux meter placed in the incubator. The radiant flux was not measured. Bulbs are changed every 800 hours.

EFFECTIVENESS OF PHOTOTHERAPY

The following criteria were used to judge the effectiveness of phototherapy: frequency of kernicterus found at autopsy, number of exchange transfusions necessary, and mean plasma bilirubin levels.

RESULTS

Of 8,693 low-birth-weight infants received by the Center from 1954 to 1971, 2,049 died, of which 1,923 autopsied.

KERNICTERUS

Table 2 shows the decrease of kernicterus at autopsy. The first period (1954–58) serves as a control since no preventive treatments for kernicterus were used, except in the case of Rhesus incompatibility (excluded from this study). From 1959 to 1965 (second period), exchange transfusions were performed whenever the bilirubinemia exceeded 20 mg/100 ml. Beginning in 1966 (third period), phototherapy was often prescribed in addition to exchange transfusions, and beginning in 1968 the majority of cases were managed by light therapy, that is, 1,872 out of 2,832 admissions for the period 1968–71. There is a highly significant decrease in the frequency of kernicterus at autopsy between the first and third periods ($p<0.001$).

TABLE 2. *Decreasing frequency of kernicterus at pathologic examination*

Year	Treatment	No. of autopsies	Kernicterus	
			No.	Percent
1954–58	0	694	30	4.8
1959–65	Exchange transfusion [1]	806	16	2
1966–71	Phototherapy plus exchange transfusion [1]	423	3	0.7

[1] Regularly performed to prevent bilirubin levels achieving or exceeding 20 mg/100 ml.

Exchange Transfusions

The percentage of exchange transfusions performed on infants with hyperbilirubinemia reaching or surpassing 20 mg/100 ml decreased significantly after phototherapy was initiated, as shown in table 3. The effectiveness of phototherapy is further emphasized by a comparison of frequency of kernicterus at autopsy in newborns treated by two different therapeutic regimens, as shown in table 4. One group was treated with ACTH and exchange transfusions, while the other was managed with phototherapy in conjunction with exchange transfusions. As compared with untreated infants of corresponding birth weights, the former regimen significantly decreased the frequency of kernicterus ($p<0.02$), in infants weighing more than 1,500 g at birth, while the use of phototherapy coincided with the disappearance of this condition in infants weighing less than 1,500 g at birth.

TABLE 3. *Decreasing frequency of exchange transfusions performed*

Year	No. of babies admitted	Exchange transfusion		
		No.	Percent	p
1959–65	3,538	211	6	0.001
1966–71	2,832	80	2.9	

TABLE 4. *Frequency of kernicterus in low-birth-weight infants*

Year	Treatment	Birth weight below 1,500 g		Birth weight over 1,500 g	
		Kernicterus/ autopsies	p	Kernicterus/ autopsies	p
1954–58	0	19/441	—	11/253	—
1959–65	ACTH plus exchange transfusion	13/519	*ns*	3/287	<0.02
1966–71	Phototherapy plus exchange transfusion	0/283	<0.01	3/140	*ns*

Development of Bilirubinemia

The incidence of bilirubinemia of 18, 20, and 22 mg/100 ml in newborns of comparable term, weight, and clinical condition was compared in light-treated and untreated babies. Results are shown in table 5.

COMMENTS

Phototherapy is clearly effective in ameliorating hyperbilirubinemia in premature infants, as indicated by the results presented. The introduction of this technique in our clinic coincided with a sharp decrease in the frequency of kernicterus at autopsy, exchange transfusions, and hyperbilirubinemia in general. Exchange transfusions did not prevent kernicterus in prematures weighing less than 1,500 g, because bilirubinemia has

TABLE 5. *Effect of phototherapy on hyperbilirubinemia*

Bilirubin level	Group		p
	Control [1]	Light treated [2]	
18 mg/100 ml	37	29	<0.05
20mg/100ml	21	11	.01
22mg/100ml	8	0	.01

[1] $N=145$.

[2] $N=183$.

already surpassed critical levels when this technique was applied. Phototherapy, on the other hand, greatly reduced kernicterus by keeping serum bilirubin levels below 15 mg/100 ml.

Light treatment was not the only therapeutic technique introduced for the treatment of hyperbilirubinemia in low-birth-weight infants over the course of this study. Other factors, too, could have contributed to the diminution of hyperbilirubinemia and kernicterus.

As an example, table 6 presents a comparison of the number of bilirubinemias greater than 18 mg/100 ml in newborns treated over a 6-year period. A significant diminution ($p<0.001$) is observed between the periods 1969-70 and 1971-72, for which the only therapeutic difference was early feeding. This technique, which has a well-documented effect on bilirubinemia is begun between the third and fifth hours of life and involves the feeding of 50 to 60 calories per kilogram per day of which 2 grams per kilogram per day are protein. The effectiveness of phototherapy is emphasized in table 6 by the significant decrease ($p<0.001$) between the periods 1966-67 and 1968, when the only therapeutic difference was a greatly increased use of phototherapy.

TABLE 6. *Frequency of hyperbilirubinemia, effect of phototherapy, and other factors*

Year	No. of babies	Bilirubin levels over 18 mg/100 ml	
		No.	Percent
1966–67 [1]	1,269	89	7
1968 [2]	640	17	2.7
1969–70 [3]	1,432	32	2.2
1971–72 [4]	1,446	18	1.2

[1] Phototherapy of 472/1,269 babies. Correction of base deficit exceeding 1 milliequivalent (meq)/100 ml.

[2] Phototherapy of 510/640 babies. Correction of base deficit exceeding 1 meq/100 ml.

[3] Phototherapy of 1,046/1,432 babies. Correction of all base deficits and hypoglycemias.

[4] Phototherapy of 1,070/1,446 babies. Correction of all acidosis and hypoglycemias; early feeding.

SIDE EFFECTS OF PHOTOTHERAPY

The side effects of this technique have been previously described and fall into two categories: immediate, or short-term side effects, which are in general easily avoided, and long-term effects, which are less well defined.[18] Information as to the chemical nature and potential pathogenicity of bilirubin photocatabolites as well as to their mechanism of action is incomplete.

We would, therefore, like to report several practical observations, the fruit of 11 years of experience in treating 3,851 newborns by phototherapy at a center for low-birth-weight infants.

Immediate Side Effects

There have been no serious side effects observed immediately upon use of phototherapy: no ocular lesions, no cutaneous burns, no secondary anemia. On the other hand, we have observed several well-known minor effects: cutaneous erythemas are observed with the same frequency as in untreated infants: cutaneous pigmentation, which subsequently disappears without sequelae has been observed in infants treated for more than 3 days; loose green stools, without any changes in feeding habits or weight loss, have occurred also.

To avoid the problem of hyperthermia due to constant light exposure, incubators were adapted to an automatic temperature regulation system controlled by skin temperature, resulting in decreased incubator heating. The liquid ration of infants under phototherapy was increased by 10 percent.

Long-Term Side Effects

Evaluation of Effects on Growth and Cranial Circumference

Since previous reports indicated that phototherapy may retard the growth of animals [12] and infants,[9] especially in regard to cranial circumference, we undertook a clinical study in order to evaluate the effect of light treatment on these parameters.

The length and cranial circumference of 97 infants managed by phototherapy were compared with those of 54 untreated infants in a purely retrospective study. All infants had been admitted to the Center during the same period, and the nursing and diet were the same for both groups. None of the infants included in the study had severe respiratory, neurologic, or metabolic pathologies. None received any hormonal treatment. The average bilirubin level before phototherapy was the same in both groups. Length and cranial circumferences were measured at 1, 2, and 3-5 years after leaving the Center during the course of followup visits.

Results were compared with Sempe's [16] established norms, and growth retardation was considered as being more than one standard deviation below the mean.

Results

The mean length of all infants admitted to the Center is just significantly below normal ($p<0.05$ at 1 year). On the other hand, as shown in table 7, a significant difference appears when true prematures are considered separately from small-for-dates babies. Infants whose intrauterine growth has been retarded, whether premature or not, do not exhibit further growth retardation upon receiving light treatment as compared to their untreated control group. This is probably due to the fact that normal growth capacity in these infants has already been compromised by other factors.[17]

Growth retardation in premature babies is a regressive phenomenon, as shown in tables 7 and 8. The size difference between light-treated and untreated infants, while highly significant at 1 year ($p<0.001$), is less significant at 2 years ($p<0.05$), and becomes statistically insignificant between 3 and 5 years. As for cranial circumference, it is only significantly different at 1 year of age ($p<0.02$), after which no difference is observed.

We then considered the possibility that growth retardation depended, in part, on the maximum bilirubinemia attained. To test this hypothesis, the control and light-treated groups were further broken down as to those infants whose bilirubinemia had exceeded 12 mg/100 ml and those whose bilirubinemia had not. When comparing sizes of infants within the control or within the treated groups, no difference was detectable on the basis of maximum bilirubinemia attained.

TABLE 7. *Growth retardation in premature and small-for-date babies*

Type of baby and age	Light treated		Control		*p*
	No.	Growth retardation	No.	Growth retardation	
Premature					
1 year	70	29	19	2	0.001
2 years	68	18	22	1	.05
3–5 years	66	13	24	0	*ns*
Small-for-dates					
1 year	27	13	30	17	*ns*
2 years	27	11	30	9	*ns*
3–5 years	22	9	29	11	*ns*

TABLE 8. *Reversible character of growth retardation in light-treated premature infants*

Age	Growth retardation
1 year (A)	29/70
2 years (B)	18/68
3–5 years (C)	13/66

Note.—Difference between A and B is significant ($p=0.05$); between B and C is not significant; and between A and C is significant ($p<0.01$).

Comments

The growth-retarding effects of phototherapy have previously been reported in animals and in man. In Gunn rats, Ballowitz et al.[12] have shown significant growth retardation of young animals exposed continually to light. Hodgman and Teberg[9] found significant statural retardation within a group of light-treated infants as compared to controls. As in our study, they found that the size difference tends to decrease with age, and the faster growth rate of treated infants should permit them to attain normal size. Lucey,[11] on the other hand, observed no significant statural retardation at all in his study of light-managed babies.

We feel that the present study, despite its limitations (retrospective nature of the study, insufficiently prolonged surveillance, small number of cases studied), nonetheless confirms the transitory nature of growth retardation of light-treated infants. Furthermore, it shows the significance in distinguishing two groups among low-birth-weight infants considered for phototherapy: the true prematures and the small-for-dates infants. The long-term reaction to light therapy of these two groups is effectively quite different.

We will not attempt to interpret the physiopathological phenomena involved, limiting ourselves to a purely clinical study. It is quite possible that the growth effects are not isolated: An action on the genital system has been reported,[16] although our data neither confirm nor deny this possibility.

CONCLUSION

Results are presented of 7 years clinical experience of the phototherapeutic management of over 3,500 low-birth-weight newborns. No accidents attributable to the phototherapy have occurred, whereas positive results have been obtained as measured by the reduced frequency of kernicterus at autopsy, decreased number of exchange transfusions performed, and general diminution of hyperbilirubinemia.

A limited study comparing length and cranial circumferences of 97 light-treated and 54 control infants confirmed the following points: Phototherapy retards the growth of true prematures but not small-for-dates infants; the retardation can be attributed to the phototherapy itself and is independent of maximum bilirubinemia attained; and, while very significant at 1 year, size difference becomes less significant at 2 years, and disappears after the third year, indicating accelerated growth of light-treated infants.

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Discussion

Dr. Ostrow: Dr. Ploussard, I would like to ask, Do you think that it is possible that the bandaging of the eyes is causing the changes in growth that you have observed? I have never discussed this, but I just wondered.

Dr. Ploussard: I do not think so.

Dr. Anderson: I have doubts about the validity of your statistics; I think we have learned over the years that analysis of effectiveness of any treatment, using the time sequential analysis (i.e., using as a control what happened 10 years ago) is extremely dangerous. In the course of the 10-year span that you analyzed, obviously a lot of things have improved other than phototherapy. You are more aware of the threat. I do believe that unless there is a very careful screening, the statistics probably would not stand up because there would be so many other parameters that would enter into the biometrical analysis of the data.

The other question that I have is, What are the controls? This, of course, is a key point. Were control babies without jaundice, or were these babies who had been treated by other means? We have to know this before we can conclude anything concerning the light. We need proof that all the other parameters were absolutely equal. Basically we ought to have a randomized sample, which you did not have. Even if you do not have a randomized sample, if you can relate all the other factors, the statistics may be valid. But you have to tell us what those statistics were.

Dr. Ploussard: As I said, in the two groups, the nursing, the weight of the infants, the term, and the maximum bilirubin before the treatment was started were the same in both groups. It depended only on the fundamentality of phototherapy. One baby or the other received phototherapy.

Dr. Schmid: In other words, all the babies had bilirubin. You treated half; what did you do with the other babies, an exchange transfusion?

Dr. Ploussard: We exchanged.

Dr. Karabus: I would like to ask a question about the low-birth-weight infants. You mentioned the indication for using phototherapy on certain bilirubin levels. If one assumes that light might have an effect on growth, presumably the size of the infant might have some effect on the amount of light that the baby absorbs. Could you say anything about the differences in the low-birth-weight as opposed to the larger infant?

Dr. Zuelzer: I have a question, and it is somewhat along the lines of Dr. Schmid's, but pertaining to anatomical parameters. You say that the incidence of kernicterus changed during the treatment period. Was this determined grossly or with the use of pathological studies?

Dr. Ploussard: With the use of pathological studies.

Dr. Zuelzer: Where you have no visible jaundice of the brain?

Dr. Ploussard: With pathological examination.

Dr. Brown: How do you make a histologic diagnosis of kernicterus in the absence of bilirubin staining?

Dr. Ploussard: I cannot answer.

Dr. Miller: Is it possible to do that?

Dr. Zuelzer: Kernicterus, or, to use the more recent designation, bilirubin encephalopathy, is a process of necrosis of ganglion cells associated with the presence of intracellular bilirubin. Leaving aside the question whether the toxic effect of bilirubin may be reversible when exposure to the pigment is of short duration, necrosis amounts, of course, to a permanent loss. The gross recognition of kernicterus by definition depends on the presence of pigment in the characteristic locations. The pigment, however, may be reabsorbed, and this may happen as a result of therapeutic procedures or may be spontaneous over a period of time, in parallel with the subsidence of hyperbilirubinemia. When this has occurred, the necrotic ganglion cells will be visible as such for a short period of time, and one may see neuronophagia and beginning gliosis about such cellular lesions. One may also see pigment deposited within the macrophages in areas of neuronal necrosis. Eventually the dead ganglion cells will disappear altogether and there will be a deficit of ganglion cells in the affected areas, whether or not it is associated with a glial response. At that stage, the neuropathologist, depending on the extent of the loss, will have to make a careful appraisal of the cellularity of the area in question in order to recognize minor degrees of permanent damage; major degrees will usually be readily apparent from the dearth of ganglion cells. In short, kernicterus is, by definition, a process associated with staining, but bilirubin encephalopathy will leave a residue that can be demonstrated when the pigment has long since disappeared.

Dr. Vogl: I would like to address a question to the clinicians present. If we assume Dr. Ploussard's statistics, and accept that the light-treated infants had growth retardation during the first 2 years and caught up during the second 2 years, I would like the clinicians' opinion of whether retardation in growth in the first 2 years and the subsequent type of growth in the following 2 years is developmentally satisfactory as a normal growth pattern?

Dr. Behrman: Dr. Johnson, would you like to make a comment about that?

Dr. Johnson: The earlier interference with growth occurs, the greater the potential for permanent damage. The period of greatest vulnerability is during gestation and the early months after birth. Whether permanent damage results, in spite of catch-up growth, depends on severity of the insult, of course. I am certainly disturbed by Dr. Ploussard's statistics.

I think that Dr. Ostrow's comment about what is causing growth retardation, if indeed there is any, is interesting. Does blindfolding the eyes change the amount of light stimulation of the pineal and indirectly influence thyroid function, for example? Also, does the eye bandage only cover the eyes, or does it also somewhat cover the head? Light penetration into the baby's skull and into the pineal itself is probably considerable. In humans, however, I believe, as in rats, the pathway of excitation to the pineal is by way of the retina. We have done some very preliminary studies looking into these matters, wondering about a possible influence of phototherapy on protein binding of the thyroid hormones or on pineal stimulation. We have not found any influence at either level. Both could theoretically affect thyroid metabolism.

Dr. Behrman: Does your data separate the small-for-term from the truly premature infant?

Dr. Johnson: You mean with reference to our 1-year followup? No. We have such small numbers as yet. But, I do not offhand, recollect any small-for-dates infants in the group.

Dr. Behrman: Then, I do not think that they mean anything.

Dr. Johnson: But we have separated them into weight groups, and, at 1 year find absolutely no difference in weight, height, occipitofrontal circumference, or developmental quotient, or in the figures on either gestational age or chronological age. The numbers are so small they do not mean much, however.

Dr. McDonagh: Do you have the figures for a blue-light-treated group?

Dr. Ploussard: All the babies were treated by blue light therapy.

Dr. Brown: Dr. Ploussard, with regard to the small-for-gestational-age term baby, he is less likely to be severely hyperbilirubinemic for weight than is a preterm baby. Did you find a difference in the length of time that the babies were exposed to light for hyperbilirubinemia when they were small for gestational age as opposed to those who were premature?

Dr. Ploussard: I have not studied that at this point.

Dr. Brown: Since there was a statistical difference within a group, then all preterm babies did not show a relative deficiency in growth, just some of that group?

Dr. Ploussard: Yes.

Dr. Brown: And there is no characterization in terms of duration of light therapy within that group that would help you focus on a particular influence.

Dr. Behrman: With regard to Dr. Ostrow's comment, I am not sure that we need to involve the retina or the pineal. We may be dealing with a very superficial matter of just handling. I am not sure that a baby who has a blind on is not handled any less than a baby who is not. I think that they need to get more attention. That may be a totally different level, and unrelated.

Dr. Hodgman: I have two questions that I wanted to ask Dr. Ploussard.

The first is, do you know the intake of your infants regarding the amount of calories or formula?

Dr. Ploussard: Yes, we know.

Dr. Hodgman: I was fascinated to discover that you are using this light as a therapy and not a preventive measure, and 75 percent of the babies became sufficiently jaundiced for you to be disturbed about it. This is a huge figure.

Dr. Ploussard: I have no explanation.

Dr. Johnson: You raised the question of possible danger to the eyes. Dr. Hodgman, do you believe that there is any danger?

Dr. Hodgman: No one has shown any danger to the retina in human infants.

Dr. Johnson: I thought that there was a report from the West Coast of a blind baby referred from an outlying hospital where they were treating it with phototherapy without shields. Is this just rumor?

Dr. Hodgman: I am not aware if it is rumor or not.

Dr. Lucey: I wrote to the doctors named and they denied any knowledge of this.

Dr. Behrman: Dr. Landes, would you like to make a comment with regard to the use of light in nurseries in military facilities?

Dr. Landes: I performed a survey of the Army hospitals in 1972 to try to determine the criteria used for phototherapy on the newborns. I found, to my surprise, quite a large variation running anywhere from zero to a high of 28 percent of babies being treated with phototherapy. The average percentage of babies treated was 8.9 percent of all live births. This amounts to a large number of babies, considering the fact that we have approximately 50,000 deliveries annually—about 4,500 to 5,000 babies each year being treated with phototherapy.

Dr. Johnson: At what level of serum bilirubin did you start phototherapy?

Dr. Landes: I attempted to find out what levels were being used to initiate phototherapy. The levels varied widely. People used different criteria with different babies, depending on whether it was premature, full term, or ill.

Dr. Behrman: Do you have a slide of that data?

Dr. Landes: I do not have a slide with me. In general there was a fair amount of agreement on full-term healthy babies who were jaundiced. Respondents generally used a value of 15 milligrams percent for these babies to initiate the phototherapy. A great many of the individuals discontinued the therapy when they saw a plateau in the bilirubin. A few of them did not discontinue the therapy until bilirubin levels of 10 milligrams percent were reached. Some physicians discontinued therapy after two consecutive declining values were obtained.

Dr. Behrman: I have had one interesting matter brought to my attention with regard to the question of the effect of light on the eyes—an article entitled "Long-Term Effect of Phototherapy on Visual Function" by Dobson, Cowett and Riggs (*J. Pediatric*, 86,555,1975). These investigators had a followup of a small group of infants with the information on the intensity of light. They have documented the intravisual examination and found that there was no detectable adverse effect on the basis of the material that they had. You might want to look at that.

Dr. Johnson: Were the eyes covered?

Dr. Behrman: I cannot tell from the abstract.

Clinical Use of Phototherapy With Emphasis on Acute and Long-Term Effects on Growth

Joan E. Hodgman, Paul Y.K. Wu, and Annabel J. Teberg

Although phototherapy has enjoyed wide use in the United States for the treatment of jaundice in the neonate since its introduction in 1968, a number of questions remain unanswered for this therapeutic agent. Risk-benefit data, particularly for long-term effects, have not been developed. Two controlled studies using phototherapy to prevent hyperbilirubinemia in the low-birth-weight infant with 2-year followup have been completed in our nurseries. During the second study, acute measurements of growth and weight gain, which were suggested by results in the first study, were performed. Metabolic measurements were made on additional low-birth-weight infants during phototherapy in an attempt to explain the effects on acute weight gain noted in study 2. All of these studies [1–6] are summarized here to give an orderly picture of acute and long-term effects of phototherapy as determined by our investigations.

PHOTOTHERAPY UNIT

A light cradle with ten 20-watt cool fluorescent bulbs designed to fit over an incubator was used for both studies (figure 1). The lights are unshielded and always used with an incubator with a cover made of Plexiglas G, which is standard equipment on all commercial incubators. Measurements of irradiance at the level of the infant within the incubator were made using a Kendall Mark IV Total Radiometer [7] (table 1). Total irradiance was 1.42 milliwatts per square centimeter. Irradiance below 360 nanometers was neglible, a small amount of near ultraviolet was recorded; and 17 percent of the total irradiance was in the 420 to 460-nanometer wave band, which is thought to be most effective for breakdown of bilirubin.

EFFECT ON NEONATAL JAUNDICE

Two separate studies were carried out, one in 1968–69 and the second in 1970–71, using a similar study design.[1,3] Infants of 1,250–2,000 grams birth weight were selected for study if they were free of congenital defects that would interfere with growth and if the Coombs' test performed on the cord blood was negative. Infants were randomly assigned to continuous phototherapy or control groups in the first study. An intermittent group with

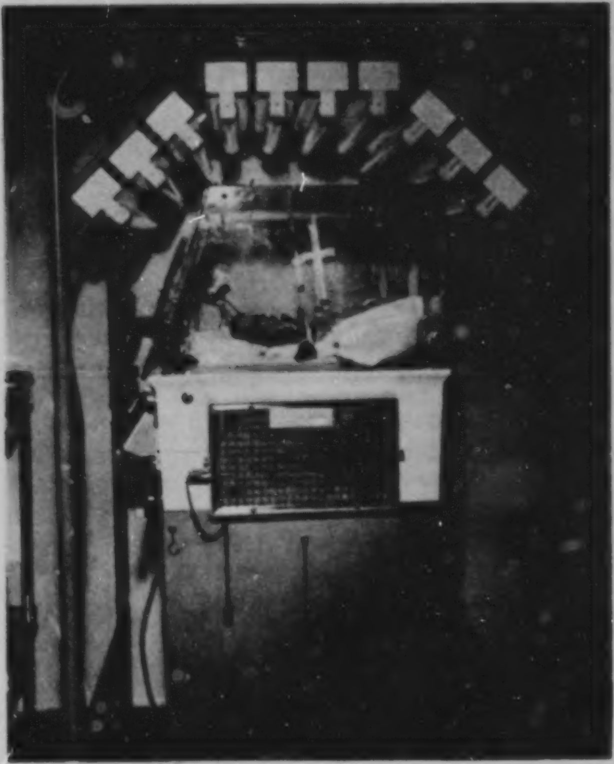

FIGURE 1. Light cradles used for both nursery studies showing position of incubator and infant.

TABLE 1. *Irradiance measurements at infant level inside C86 Isolette incubator*

Wave band (nanometers)	Irradiance [1] (milliwatts per square centimeter)
Below 360	0.001
360–420	0.115
420–460	0.245
460–500	0.227
500–650	0.484
Above 650	0.348
Total	1.420

[1] Measurement of irradiance was made with a Kendall Mark IV Total Radiometer with filters and monochrometer paper.

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lights on for 12 hours between 8 a.m. and 8 p.m. and off for 12 hours was added in the second study. Phototherapy was started at 24 ± 12 hours and continued for 5 days. Patient population for the two groups is summarized in table 2.

TABLE 2. *Patient population*

Study	No.	Birth weight (mean per grams)	Gestational age (weeks)
1 (1968–69):			
Continuous	47	1,695	34.4
Control	51	1,690	34.3
2 (1970–71):			
Continuous	40	1,766	34.2
Intermittent	40	1,681	33.8
Control	40	1,760	34.0

Daily total bilirubin levels for the first study are presented in graphic form in figure 2, and for the second study in figure 3. Peak bilirubin levels from both studies are summarized in table 3. Continuous phototherapy was consistently effective in preventing elevation of the bilirubin above 15 milligrams percent. Mean values in both studies were significantly lower than controls from day 2 through day 6. Intermittent phototherapy on a 12-hour-on, 12-hour-off schedule was also effective in maintaining lower bilirubin levels, but not as effective as continuous therapy. Mean bilirubin levels were significantly different from controls for day 3 through day 5,

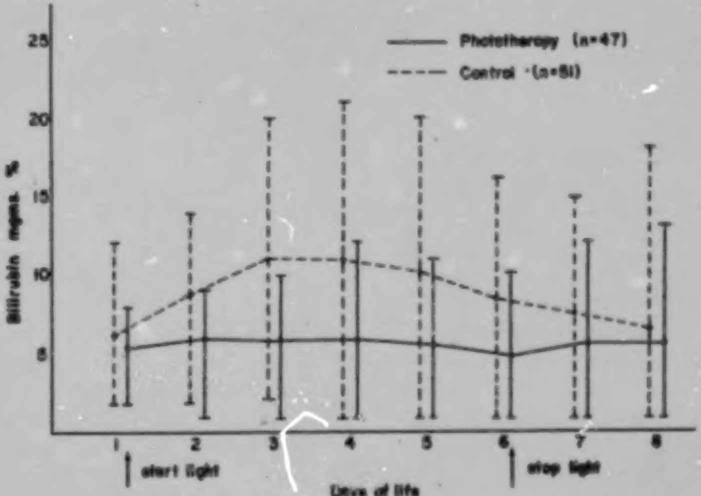

FIGURE 2. Mean and range of total daily bilirubin levels in study 1.

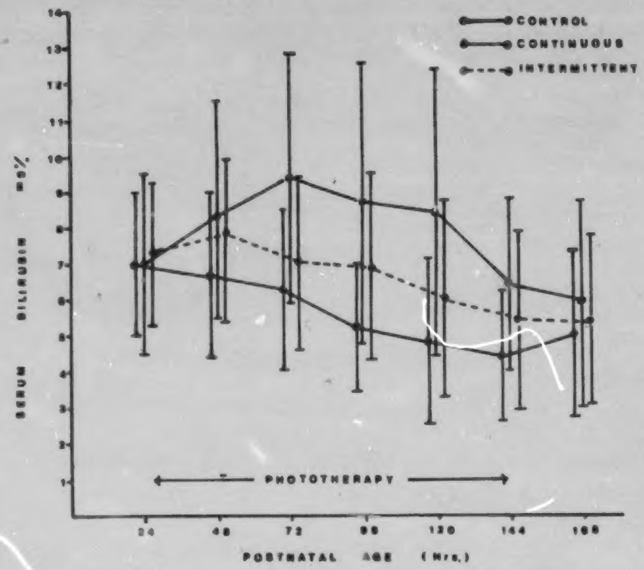

FIGURE 3. Mean plus or minus 2 standard deviations of total daily bilirubin levels in study 2. (Reprinted with permission from the *Journal of Pediatrics.*[2])

TABLE 3. *Peak bilirubin levels*

Study	Total cases	Bilirubin (>12 mg%)		Bilirubin (>15 mg%)		Exchanges	
		No.	Percent	No.	Percent	No.	Percent
1:							
Control	51	29	57	13	25.5	3	6
Continuous	47	2	4	0	0	0	0
2:							
Control	40	14	35	5	12.5	0	0
Intermittent	40	3	7.5	1	2.5	0	0
Continuous	40	2	5	0	0	0	0

Note.—mg% = milligrams percent.

and values for continuously treated infants were significantly lower than those for intermittently treated on day 4. The difference in control values in the two studies is of considerable interest and reflects changes in nursery routines between 1968 and 1970. These include a move to nurseries with more daytime ambient light, earlier initiation of feeding, and more liberal use of parenteral fluids in the premature infants.

The population served by our hospital includes black infants as well as Spanish-American-surnamed infants, primarily of Mexican extraction.

Daily bilirubin levels from the first study by racial group are presented in table 4. Although peak bilirubin levels are higher in the infants of Spanish-American surname in both control and treated groups, the differences are not significant, and therapy in the darker skinned infants was clearly effective.

TABLE 4. *Daily bilirubin levels by racial groups: Study 1*

Day	Phototherapy			Control		
	C (*N*=12)	B (*N*=18)	SA (*N*=15)	C (*N*=13)	B (*N*=24)	SA (*N*=13)
1	5.9	5.2	5.3	6.5	5.5	6.5
→						
2	5.8	6.0	5.5	9.4	8.2	9.8
3	5.6	6.0	5.7	11.8	9.8	12.2
4	5.2	5.6	6.2	12.2	9.6	12.2
5	5.0	5.2	6.0	10.7	9.1	11.3
6	4.5	4.7	5.1	8.8	7.6	9.6
→						
7	5.3	5.1	5.5	8.3	6.5	8.4
8	5.0	5.2	6.1	7.0	5.7	7.2
Peak	6.4	6.7	7.7	12.6	11.0	13.5

Note.—→= Start and end of phototherapy; C=Caucasian, B=Black, SA=Spanish-American surnamed.

ACUTE EFFECTS ON GROWTH

During the second study, length and head circumference on all infants were measured weekly for the first 4 weeks by one observer.[2] Physical examination including neurologic assessment was also performed. The weight at 7 days was compared to the weight at birth for each infant. The infants were divided into two groups: those whose weight equalled or exceeded birth weight and those who were below birth weight. All infants were fed equivalent amounts per unit weight of isocaloric formula. If the infant was unable to suck effectively, the appropriate amount of formula was given by gavage. The numbers of infants in each treatment group and the mean difference from birth weight are shown in table 5. The number

TABLE 5. *Weight on the seventh day compared to birth*

Phototherapy group	Infants who gained weight			Infants who lost weight		
	No.	Percent	Grams Gained (*M*±*SD*)	No.	Percent	Grams Lost (*M*±*SD*)
Control	32	80	97.3±76.4	8	20	83.3±57.9
Intermittent	22	58	105.3±77.7	16	42	[1] 52.7±45.1
Continuous	16	44	90.9±74.5	20	66	85.0±61.4

[1] $p = < 0.05$ compared to control.

Note.—*M*=mean, *SD*=standard deviation.

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of infants above and below birth weight by the seventh day was clearly related to phototherapy.

In the control group, 80 percent of infants had equalled or exceeded birth weight as compared to 58 percent of infants treated intermittently and 44 percent of infants treated continuously. The amount of weight gained or lost did not differ significantly except for the intermittently treated infants whose weight loss was less than controls. Significantly fewer infants in both treated groups had regained birth weight by 7 days, however. Net weight gain during each of the subsequent 3 weeks is presented in table 6.

TABLE 6. *Weekly increments in body weight in grams*
[Mean ± standard deviation]

Week	Control		Phototherapy			
			Intermittent		Continuous	
	No.	Weight gain	No.	Weight gain	No.	Weight gain
2	36	139.0±69.8	37	[1] 193.6±82.3	34	[1] 184.5±55.5
3	29	162.4±62.3	29	[1] 195.5±74.2	32	[1] 225.3±62.5
4	21	161.7±82.7	21	179.4±63.1	22	168.1±103.9

[1] $p = <0.05$ compared to control.

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By the fourth week, all three groups were gaining at an equivalent rate. Changes in length and head circumference showed similar patterns (tables 7 and 8). In spite of the same fluid and caloric intake by weight, the treated infants did not grow as rapidly as controls while under phototherapy, but appeared to experience catch-up growth in the succeeding 2 weeks.

Daily hematocrits in the three groups for the first week are presented in table 9. A gradual decrease in all groups is observed with no intragroup differences. Daily blood glucose for the same period are shown in table 10. Values were stable within accepted normal limits in all groups. The value

TABLE 7. *Weekly increment in head circumference in centimeters*
[Mean ± standard deviation]

Week	Control	Phototherapy	
		Continuous	Intermittent
1	0.5±0.3	0.4±0.4	0.7±0.6
2	0.7±0.4	[1] 0.9±0.4	0.6±0.3
3	0.9±0.4	0.8±0.5	1.0±0.5
4	0.9±0.5	1.1±0.4	0.9±0.6

[1] $p = <0.05$.

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TABLE 8. *Weekly increment in crown-heel measurements in centimeters*
[Mean ± standard deviation]

Week	Control	Phototherapy	
		Continuous	Intermittent
1	1.2±0.9	[1] 0.8±0.7	0.9±0.7
2	0.6±0.5	0.8±0.6	0.8±0.6
3	0.6±0.5	0.9±0.7	0.7±0.5
4	0.8±0.7	0.7±0.6	0.6±0.4

[1] $p=<0.05$.

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TABLE 9. *Daily hematocrit in milligrams percent*
[Mean ± standard deviation]

Hours	Control	Phototherapy	
		Continuous	Intermittent
24	56.1±9.9	55.1±9.7	53.8±9.3
48	54.6±7.8	54.2±7.8	55.1±8.1
72	52.3±7.6	51.4±8.0	52.6±6.2
96	51.5±8.1	50.4±8.5	51.4±7.1
120	50.0±7.9	49.8±7.8	50.1±8.4
144	48.8±8.9	48.2±9.9	48.9±8.2
168	48.1±9.2	48.1±7.6	48.4±8.1

Note.—The differences between the groups were not statistically significant ($p > 0.05$).

TABLE 10. *Daily blood glucose in milligrams percent*
[Mean ± standard deviation]

Hours	Control	Phototherapy	
		Continuous	Intermittent
24	66.4±21.6	66.7±24.0	67.5±25.1
48	66.4±21.6	61.9±28.7	60.7±15.2
72	68.1±19.4	[1] 58.3±12.2	62.4±24.5
96	68.1±19.4	67.4±25.5	70.0±27.1
120	62.9±23.3	58.9±16.4	69.9±28.7
144	68.9±17.5	66.9±19.5	71.5±18.4
168	66.2±20.6	73.4±33.2	73.8±28.1

[1] $p<0.05$ when compared to control group.

for continuously treated infants was significantly lower than controls on day 3 only. This may represent only sampling error, but coincides in time with the period of decreased weight gain in treated infants.

Neurologic response on the seventh day is presented in table 11. Tone and traction showed no differences, but Moro and suck were significantly depressed in treated groups. The decreased suck is of particular interest in view of the decreased weight gain demonstrated in infants treated with phototherapy.

TABLE 11. *Phototherapy: Neurological responses on seventh day*

Response	Control	Phototherapy	
		Continuous	Intermittent
Tone	2.1±0.7	2.1±0.9	2.1±0.8
Moro	[1] 2.7±0.7	2.3±0.8	2.5±0.6
Suck	[1] 3.3±1.0	2.8±1.1	2.9±1.1
Traction	2.0±0.8	2.0±0.9	2.1±0.8

Note.—Score: Absent = 0; poor = 1; fair = 2; good = 3; increased = 4.
[1] p = <0.05.
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INSENSIBLE WATER LOSS AND BLOOD FLOW

Insensible water loss as determined by acute changes in weight was measured in 56 preterm infants at a mean postnatal age of 4.6 days.[3] Two sets of measurements were recorded for each infant, once before, and once during, phototherapy following at least 1 hour of exposure. Two sets of studies were performed. In the first, incubator temperature was set on manual control to maintain a skin temperature of 36.5° C initially, and was not changed during the study period. Results divided by weight are presented in figure 4. Insensible water loss increased from 80 percent in the smaller infants to 192 percent in the larger infants. As shown in table 12, rectal temperature remained constant but incubator temperature increased, as did skin temperature and heart and respiratory rate. Clearly,

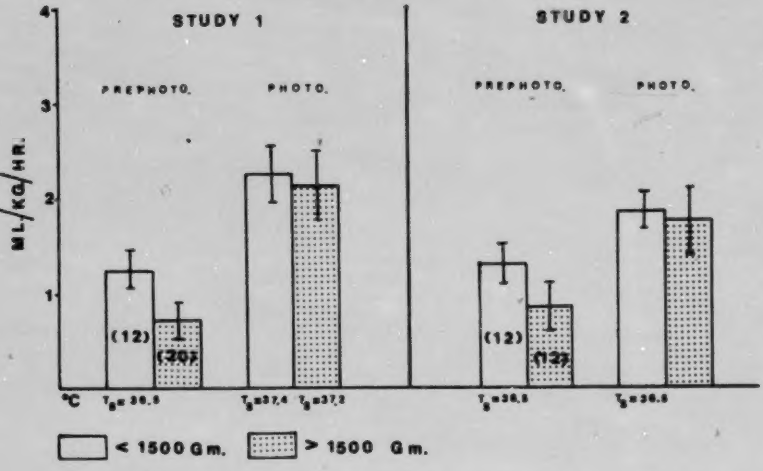

Figure 4. Changes in insensible water loss (IWL) before and during phototherapy without (study 1) and with (study 2) control of skin temperature at 36.5°C. (Reprinted with permission from *Pediatrics*.[3])

TABLE 12. *Changes in humidity, temperature, respiration, and heart rate, study 1*

Measurement	Prephototherapy ($M \pm SD$)		Phototherapy ($M \pm SD$)	
	<1,500g	>1,500g	<1,500g	>1,500g
Humidity [1]	36.6±6.1	36.5±5.8	36.1± 6.8	36.2±6.3
Skin temperature [2]	36.5±0.3	36.5±0.2	37.4± 0.3	37.2±0.3
Rectal temperature [2]	36.7±0.4	36.9±0.2	37.4± 0.2	[3] 37.1±0.3
Incubator temperature [2]	35.2±0.6	33.7±0.6	38.5± 0.3	34.2±0.5
Respiratory rate per minute	58.2±8.5	48.5±8.6	66.8± 6.8	62.0±4.2
Heart rate per minute	154.2±8.6	144.4±8.2	164.3±10.1	158.5±6.5

Note.—*M*=mean, *SD*=standard deviation, g=grams. Differences between prephototherapy and phototherapy were all significant at the 0.05 level except where noted.

[1] In percent.

[2] In degrees Centigrade.

[3] $p > 0.05$.

some of the increased insensible water loss was due to temperature effects from heating of the incubator during phototherapy. In the second study, skin temperature was maintained constant at 36.5° C before and during phototherapy. Under these conditions, insensible water loss increased 42 percent in the smaller infants and 113 percent in the larger infants (figure 4). Rectal temperatures fell slightly, but significantly, in the smaller infants, but there were no significant changes in incubator temperature and no evidence of temperature response in the infants, as shown in table 13. The increased insensible water loss in the second study during phototherapy appeared to be directly related to the effect of the lights and not to a temperature-mediated response.

Using an electro-capacitance plethysmograph, skin and muscle blood flow were measured in 20 preterm infants before and during phototherapy.[4] When the incubator was manually controlled to maintain an

TABLE 13. *Insensible water loss: Changes in humidity, temperature, respiration, and heart rate, study 2 (servo-control)*

Measurement	Prephototherapy ($M \pm SD$)		Phototherapy ($M \pm SD$)	
	<1,500g	>1,500g	<1,500g	>1,500g
Humidity [1]	36.3±5.4	38.8± 6.2	36.2±6.1	36.5± 6.1
Skin temperature [2]	36.5±0.25	36.5± 0.2	36.5±0.3	36.5± 0.25
Rectal temperature [2]	37.0±0.25	37.1± 0.4	[3] 36.6±0.3	37.0± 0.2
Incubator temperature [2]	35.4±0.4	33.5± 0.4	34.8±0.8	32.8± 0.5
Respiratory rate per minute	56.4±8.2	48.5±10.2	58.2±6.6	52.4± 9.5
Heart rate per minute	150.4±8.8	148.4± 8.2	152.4±9.2	148.2±12.4

Note.—*M*=mean, *SD*=standard deviation, g=grams. Differences between prephototherapy and phototherapy were not significant except where noted.

[1] In percent.

[2] In degrees Centigrade.

[3] $p < 0.05$.

initial skin temperature of 36.5° C and not altered during the study, total blood flow increased by a mean of 116 percent due primarily to increased skin blood flow and to a lesser extent to increase in muscle blood flow (figure 5). When the incubator was servo-controlled to maintain a skin temperature of 36.5° C during the study, total blood flow increased to a lesser degree, due entirely to changes in skin blood flow (figure 6). An increase in skin blood flow accompanied by an increase in insensible water loss appears to be a direct effect of phototherapy independent of effects of changes in temperature. An associated increased metabolic rate is suggested by the delay in weight gain during phototherapy followed by catch-up gain noted in the second group of infants as outlined above. The caloric requirements during phototherapy require direct study for confirmation. We recommend an increase in both total fluid and caloric intake during phototherapy to offset the increased requirements demonstrated by these studies.

FOLLOWUP

Developmental performance was assessed in the first group of infants using Gesell Development scores [8] by one of the authors (A.T.) without prior knowledge of nursery therapy (table 14).[5] The median scores and range were the same for both treated and control infants, and when corrected for prematurity, both groups were performing at a normal level.

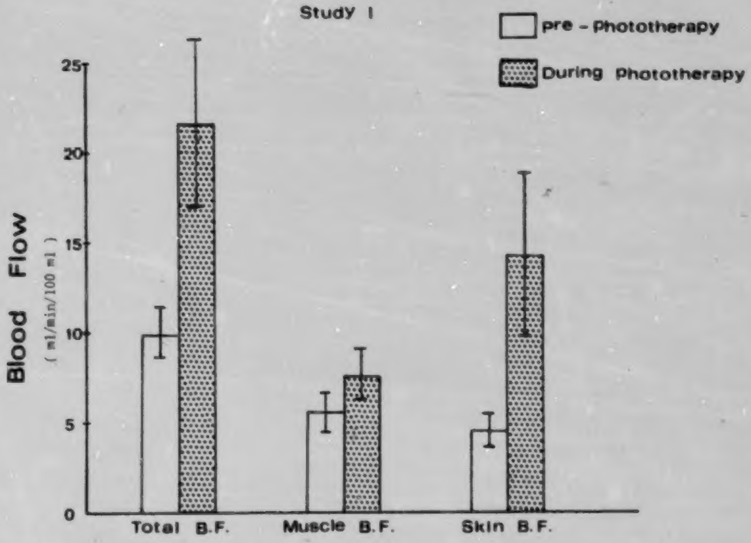

FIGURE 5. Changes in blood flow before and during phototherapy in study 1 without controlling skin temperature. (Reprinted with permission from *Pediatric Research*.[4])

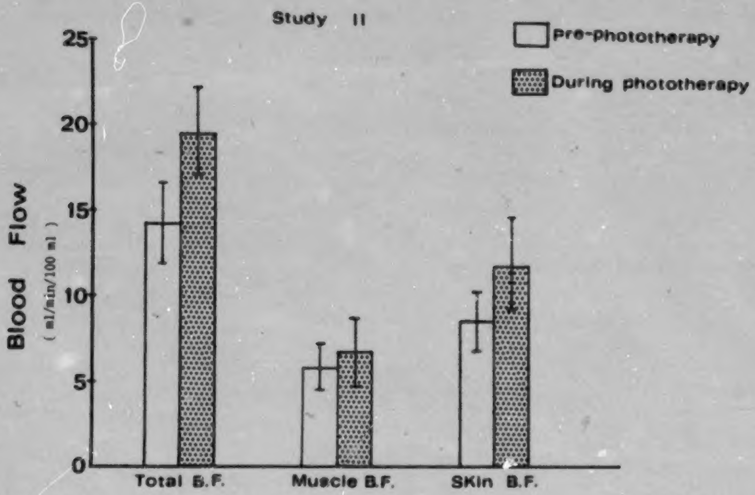

FIGURE 6. Changes in blood flow before and during phototherapy in study 2 when skin temperature was controlled at 36.5° C. (Reprinted with permission from *Pediatric Research*.[4])

Neurologic performance was assessed as normal; abnormal, if neurologic changes interfered with function; and questionable, if neurologic changes such as asymmetry of muscle tone or abnormal eye signs, which did not interfere with function, were present. When neurologic and developmental performance were combined (see table 15), one infant in both treated and control groups was clearly abnormal and four in each group had questionable findings. Not only were the treated and control infants comparable, but they were performing well for a group of low-birth-weight infants.

Growth was assessed by recording percentile of expected growth for chronologic age using the Harvard Infant Growth Curves [9] for weight and length, and the Nelhaus Interracial Graph [10] for head circumference. Results for weight at birth, 1 and 2 years for group 1, are presented in table 16.[6] The distribution of birth weights using the Denver intrauterine growth

TABLE 14. *Phototherapy of the premature: Initial study—Developmental quotient at followup*

Quotient	Phototherapy (*N*=23)	Control (*N*=23)
Developmental quotient:		
Range	40–106	50–100
Median	90	89
Corrected development quotient [1]		
Range	48–116	57–112
Median	103	103

[1] Chronologic age in weeks is corrected for prematurity based on gestational age at birth.

TABLE 15. *Phototherapy of the premature: Initial study—Neurologic and developmental summary*

Group	Phototherapy		Control	
	N	D	N	D
Normal	19	21	18	18
Abnormal	0	1	1	1
Questionable	4	1	4	4
Total	23	23	23	23

Note.—N=neurologic, D=developmental.

TABLE 16. *Growth assessment for weight after phototherapy,*[1] *group 1*

Percentile	Birth		1 year		2 years	
	Light[2]	Control	Light[2]	Control	Light[2]	Control
<90	1	1		2		2
75–90	3	1				1
50–74	1	4	1	1	1	1
25–49	3	5	1	7		2
10–24	5	4	5	5	4	2
<10	10	8	16	8	9	7
Total	23	23	23	23	14	15

[1] Based on Harvard Infant Growth Curves.
[2] Continuous.

curves[11] for the treated and control infants is similar. Of particular importance, the number of small-for-gestational-age infants is equivalent. The majority of the infants are below the 50th percentile during the 2-year period as would be expected for low-birth-weight infants. Some effect of catch-up growth is apparent at 2 years. At the first-year examination, however, more light-treated infants are below the 10th percentile than

TABLE 17. *Growth assessment for weight after phototherapy,*[1] *group 2*

Percentile	Birth			2 years		
	Light		Control	Light		Control
	C	I		C	I	
>90	1			1	2	1
75–90	2		1	1	1	
50–74	2	2	4	4	4	4
25–49	1	6	5	6	3	4
10–24	8	4	5	1	6	2
<10	5	6	5	6	2	9
Total	19	18	20	19	18	19

[1] Based on Harvard Infant Growth Curves.
Note.—C=continuous, I=intermittent.

control infants, and although most infants in both groups are growing at a normal rate, this pattern is still evident at 2 years. Weight at birth and 2 years for the infants from the second study are presented in table 17.[a] Here, although the expected preponderance of small infants is again evident, the distribution by percentiles is equivalent for both treated and control infants, with the intermittent group closest to a normal distribution. The control groups in the two studies, although not concurrent in time, are also similar in growth patterns. The infants were appropriately proportioned and results for length followed the same patterns as those for weight.

Although intelligence does not generally correlate directly with head size, decreased intellectual performance does correlate with head circumference below the 2d percentile. Consequently, growth in head circumference in these infants has been of particular interest, and the results for both groups of infants are presented in table 18. At the first-year followup for group 1, more infants receiving phototherapy than control infants were below the 2d percentile. By the second year, although the treated infants were still smaller than controls, the number below the second percentile was not different. The results for the second group of infants at 2 years show similar growth in head circumference for all groups, with the continuously treated and control infants almost identical, and a slight but insignificant increase in larger head sizes in the intermittently treated group. The two control groups, although not concurrent in time are again almost identical. Infants whose growth in head circumference progressed at a normal rate demonstrated normal neurologic and developmental performance regardless of the actual percentile. Only two infants who showed deceleration of head growth were abnormal—one phototherapy treated and one control. It is unlikely that the unexplained number of small infants in the first study was due to phototherapy, since the differences were not reproducible in the second group. The differences in growth in the first group that persisted into the second year are of questionable clinical significance, since these infants are of normal proportions and are performing comparable to the controls.

CONCLUSIONS

Phototherapy is effective in the prevention of hyperbilirubinemia in the low-birth-weight infant. Continuous therapy was more effective than the intermittent schedule of 12 hours on and 12 hours off.

Metabolic requirements for fluid and calories appear to be increased during phototherapy. Whether these increased needs can be offset by therapy deserves further study.

No deleterious long-term effects of phototherapy have been found at 2-year followup.

TABLE 18. *Growth assessment for head circumference after phototherapy,[1] groups 1 and 2*

Percentile	Group 1								Group 2					
	First year				Second year				Second year					
	Continuous		Control		Continuous		Control		Continuous		Intermittent		Control	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent
>98											1	6		
50–98	3	13	7	31	4	29	10	67	10	53	11	61	9	45
2–49	14	61	15	65	7	50	3	20	7	37	6	33	9	45
<2	6	26	1	4	3	21	2	13	2	10			2	10
Total	23	100	23	100	14	100	15	100	19	100	18	100	20	100

[1] Based on Nelhaus Interracial Graph.

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Twelve Years of Standardized Phototherapy

J. Obes-Polleri, W. S. Hill, and J. J. Obes

It has been our view [1–4] on theoretical and experimental grounds that with regard to phototherapy (1) there is a direct relationship between the dose of effective irradiance and the decay rate of the bilirubin, (2) hyperbilirubinemias are individual and unpredictable dynamic systems, and (3) early initiation of phototherapy is needed if it is to be effective. On those premises we have standardized our use of phototherapy in Uruguay.

The main difficulty in the use of phototherapy lies in the unpredictability of the rate of rise of bilirubin; quite often it rises inexorably, and phototherapy may not be sufficient to prevent kernicterus. The standardization of the use of phototherapy is fundamental.[5] There is a need to measure light administered in $\mu W/cm^2$.

In order to prevent the rise in bilirubin, it is very important to start the treatment before the hyperbilirubinemia has reached substantial levels. Very early use does not necessarily mean prophylactic treatment. Since less than 20 percent of the low-weight newborns in our center need phototherapy, preventive treatment as a nursery routine is unnecessary.[3]

The initial bilirubin value should be written down on a form of the "standard graph," which indicates the cases to be treated or closely watched. From that moment this form (figure 1) constitutes the tool that will guide the clinician who plots on it an actual curve from bilirubin determinations every 6, 12, and 24 hours.

The risk of bilirubinemia depends first on its type. Individualizing is an unavoidable first step. Hemolytic (ABO/Rh) and nonhemolytic hyperbilirubinemias have different rates of bilirubin accumulation with very different potential for the success of phototherapy. The former obviously represents a much larger risk of kernicterus. Roughly, the phototherapy indications are routine use in nonhemolytic hyperbilirubinemias, cautious use in ABO hemolytic disease (where it has reduced the necessity for change), and routine use following exchange in Rh hemolytic disease, since it limits rebound and reduces the need for exchange.[5]

Even within hyperbilirubinemias of the same type, the potential for bilirubin accumulation differs considerably because the system is dynamic and complex. Thus, each crisis should be appraised and treated on strictly individual criteria.[4,5] An individual form of the "standard graph" should be

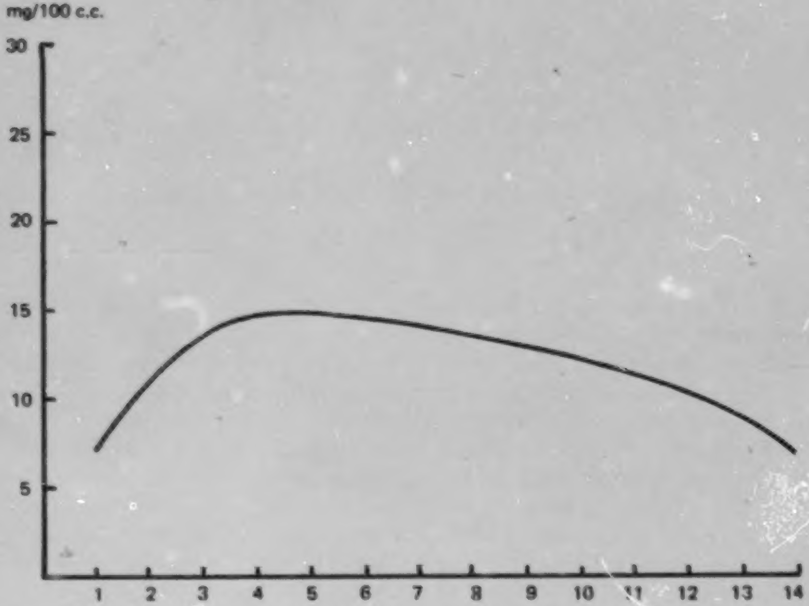

FIGURE 1. The standard graph of bilirubinemias in the low weight newborn. A guideline for phototherapy.

used for each case. The contributing factors should also be evaluated individually. Special attention must be given to the small preterm babies.

The standard graph has been derived from hundreds of untreated bilirubinemias.[3] In spite of being an actual average, reflecting a "normal" pattern of the bilirubinemia of the low-weight newborn, it should be considered only as a useful guideline. It tentatively separates a potential risk zone from one of relative safety, without establishing defined limits. Further, it only assumes the probable participation of the aggressive and dangerous fraction, unbound bilirubin.[6]

The irradiation of the maximum of corporal surface of the patient must be intensive and continuous if bilirubin level is to be prevented from rising further. The equipment to be used should possess the highest effective power compatible with environmental normality and absence of iatrogenic risk. The decrease of the hyperbilirubinemia must be achieved in the minimum of time.

There are no fixed periods of irradiation to stop the treatment, no magic number at which to stop treatment.[3,5] The guiding factor is the contrast between the actual serum bilirubin values of the infant curve and the standard graph.[2-4,7,8] This contrast is valid for the whole course of the treatment; it tells us when to begin, how long to use it, and when to stop or when it is necessary to switch to exchange. Generally, 72 hours of irradiation are enough to control hyperbilirubinemias, but the real determinant is whether the actual curve falls below the standard graph. The observation of the patient's skin has no significance. The actual serum bilirubinemia values must remain far below the risk zone.

In phototherapy there is a rebound of a different nature and importance than that following the exchange.[9] Care is needed particularly during the first 3–4 days of life, in the hemolytic hyperbilirubinemias and in the very small premature. In those cases, phototherapy, with the possible additional use of exchange, must be carried safely beyond the possibility of a rebound. Use of exchange depends mainly on the appraisal of the potential rate of bilirubin rising, and also on the contributing circumstances. The experience and knowledge of the clinician of the pathophysiology of the bilirubinemias, as well as of the immediate possibilities of bilirubin decay, are the main factors for a safe decision.

The useful wavelengths for control of bilirubin, well known by Cremer, Perryman, and Richards [10] and correctly transcribed by many of the subsequent authors, do not appear to have always been well appreciated.[11,12] Before 1962 they were experimentally studied by us, using monochromatic lights (Beckman spectrophotometer and AFGA photographic plates).[1] We located the zone of greater absorption (extinction) of the bilirubin between the 400 and 500 nanometer (nm) (blue-violet) range. It presented two main peaks, at 420 and 460 nm. The zone of transformation corresponded to the same zone. The monochromatic blue light was noticeably more active in the 460-nm peak.

As in every new therapeutical method, phototherapy has been, and must still be, subject of concern.[13,14] Its use without the proper experience must follow strict rules.[4,5]

The risks related to the phototherapy arise from two different sources often confused in clinical practice and in the concern for its safety. The first and most frequent refers to an inadequate indication or the use of an incorrect technology.[4,5,7] Much more important but less frequent, the second refers either to the failure of an appropriate use of phototherapy in neutralizing the risk of kernicterus, or to a true biological toxic effect introduced by radiations.

The iatrogenia caused by medical inexperience in phototherapy is still common, unjustly discrediting the method. Knowledge regarding the possibilities of the phototherapy and of an effective and safe standardized technology must be widely spread. Most times, any ill effects or ineffectiveness is related to improper indication, late start, undue loss of time, late switch to exchange or more commonly to a faulty technology (ineffective power, alternating light, use for a short duration, or lack of protecting eyes or to lack of clinical evaluation (anemia of hemolytic hyperbilirubinemias, etc.) Concomitant neonatal pathology may account for some ill effects attributed to light.

The intrinsic iatrogenia related to the complex biological effects of the light is still purely potential. We have never observed any personally, nor have we seen any reported indisputedly elsewhere; nevertheless it must be searched for. Two types of potential clinical iatrogenic findings must be separated: those that immediately accompany phototherapy and the long-term sequalae.

No early ill effects have been found by us when our standardized phototherapy technique was used. A well-controlled study of 100 cases did not show any ill effects at all in the first month, during or after phototherapy, on growth (weight, height, cranial circumference), on the incidence of anemia, diarrhea, and susceptibility to infection, or on the mortality rate.[4] Certain secondary side effects observed during treatment can be checked easily or can disappear by themselves without sequelae. The most frequent are overheating and skin reaction, including tanning. Only the erythema causes damaging injuries; tanning only increases the melanosomas in the melanocyte.

Tanning results from the effects from a wide zone of irradiance (320–400–620 nm). The erythema zone is 324–400 nm. As the effect is not filtered by common glass, it can, therefore, operate normally. We, like others, have observed tanning more frequently and intensely in recent years during the "early life" of special blue tubes (WF20 T12/B). This does not really matter in the face of a more effective selective power of these tubes.

The possibility of long-term harmful implications is more difficult to discard as these develop outside the neonatal field (growth retardation, gross or minimal neurologic abnormalities, learning disabilities, etc.). Our followup policy has been the following:

- All patients who have undergone phototherapy with bilirubinemias over 12 milligrams per/100 milliliters return to our neonatal center (at 3 months and again at 12 months) for clinical evaluation. We look for gross or minimal abnormalities and send the dubious cases to the pediatric neurologic departments.
- We have only occasionally had the opportunity to monitor long-term effects (neurologic examinations, electroencephalogram, and intelligence and behavior tests).

In spite of the obvious limitations of this investigation, depending on the good will of parents and clinicians of other fields, in 12 years and more than 3,500 cases (using the present clinical devices equipped with common day and blue light fluorescent tubes), we have *never* seen iatrogenia in well-indicated and correctly used phototherapy, nor has it been later reported to us.

The concern about long-term implications of phototherapy is well justified, but to make valid observations we need larger prospective controlled studies with calibrated equipment, using sophisticated techniques for early detection of abnormalities.

SUMMARY

At the present time, no long-term negative implications have been documented when phototherapy was properly applied. The theoretical concern of the National Academy of Science committee is understandable,[15] as is the proposal of a cautious use and the need for more research,[15,17] but in our view many of the expressed doubts or difficulties have been dissipated already. Our extensive clinical experience, over many years and with thousands of cases accomplished with most of the proposed reasonable recommendations concurs with Lucey's [18] final comments.

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Five Years' Experience In Phototherapy[a]

Jiro Ogawa, Yunosuke Ogawa, Shoju Onishi, Takashi Shibata,
and Hisako Saito

Phototherapy has been successfully applied for the treatment of neonatal hyperbilirubinemia for over 15 years. Although its effectiveness in lowering bilirubin levels is well established, possible untoward effects of light and the photodegradation products of bilirubin have not been investigated fully. Since 1968 we have treated 2,375 jaundiced infants with phototherapy in 12 affiliated hospitals and have investigated the mechanism of photodestruction of bilirubin and the biologic effects of illumination. This report describes our 5 years' experience of phototherapy, which will make some contributions to a better understanding of the biologic effects of phototherapy.

CHARACTERISTICS OF NEONATAL JAUNDICE IN JAPAN

The incidence of hyperbilirubinemia in Japan is much higher than reported in Western countries.[1] Since the Rh-negative population is less than 0.5 percent, hemolytic jaundice due to Rh incompatibility is rarely seen. ABO incompatible jaundice also seems to be rare, though the true incidence is unavailable owing to the lack of accurate means for its diagnosis. Jaundice due to Crigler-Najjar syndrome, glucose-6-phosphate dehydrogenase deficiency, and congenital spherocytosis are also extremely rare. Thus the majority of jaundice is classified as hyperbilirubinemia of unknown etiology. Table 1 shows the incidence of hyperbilirubinemia in full-term infants born in two of our affiliated hospitals. Twenty percent of full-term infants, otherwise completely healthy, have serum bilirubin concentrations over 15 milligrams (mg) per 100 milliliters (ml). Similarly, hyperbilirubinemia (serum bilirubin concentration over 15 mg/100 ml) is observed in 18 percent of all full-term neonates born in the other hospitals. Similar observation has been made in Taiwan.[2] The causes of this high incidence in Asian countries have not fully been investigated.

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[a] We wish to thank all the members of Department of Pediatrics, Nagoya City University Medical School for their generous cooperation. We are also indebted to the pediatric staffs in affiliated hospitals for their data included in this paper.

TABLE 1. *Incidence of hyperbilirubinemia in full-term newborn infants, 1970–73*

Peak bilirubin levels	A hospital			B hospital		
	No.	Percent		No.	Percent	
<15 mg/100 ml	2,201	81.4		1,133	79.6	
15–20 mg/100 ml	452	16.7	18.6	254	17.8	20.4
>20 mg/100 ml	52	1.9		37	2.6	
Total	2,705			1,424		

EQUIPMENT FOR PHOTOTHERAPY

The first step in phototherapy was undertaken in the development of the improved light chamber. Since the dose of light is inversely proportional to the second power of distance, it is desirable that the light source be placed not too far from the infant. Our light chamber is designed to be placed on the top of the incubator, and the distance between the light source and the infant is 30 centimeters. Figure 1 illustrates an improved light chamber being used in our institution. This contains four 20-watt blue-white fluorescent light tubes. In the center of the light chamber, a small electric fan is installed, which allows the excess heat to escape, preventing the infant in the incubator and the fluorescent light tube from overheating. Ambient temperature is kept stable when the fan is on, as shown in figure 2. Fluorescent blue-white tubes,[b] developed by Matsushita Electric Company upon our request, have characteristics in the radiation energy distribution such that the emission of ultraviolet rays is eliminated, as shown in figure 3. This elimination reduces the possible undesirable effects of ultraviolet rays to the infant, to the nursery personnel, and to the acrylic hood of the incubator. It has been known that there is a marked dropoff of energy of fluorescent lamps with use.[3] Table 2 shows the percent decrement of energy output in the blue-white fluorescent lamp (Matsushita FL20 BW–NU). Radiant energy of the tube under the conditions of use drops by 10, 16, and 24 percent after 1,000 hours, 3,000 hours, and 5,000 hours, respectively. It is important, therefore, to record the duration of use of the tube. A timer (hour-meter) is built in the light chamber for the estimation of duration of use. It is our policy currently that the fluorescent tubes be changed to new ones after 3,000 hours of use. Table 3 presents the energy distribution in the various parts of the incubator under the condition of ordinary use. Thus the infant received about 28 watts per square meter of radiant energy under the standard condition with our phototherapy unit.

FOLLOWUP STUDIES

In our institution, phototherapy has been indicated solely for the treat-

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[b] FL20 BW–NU (Matsushita Electric Co., Osaka, Japan).

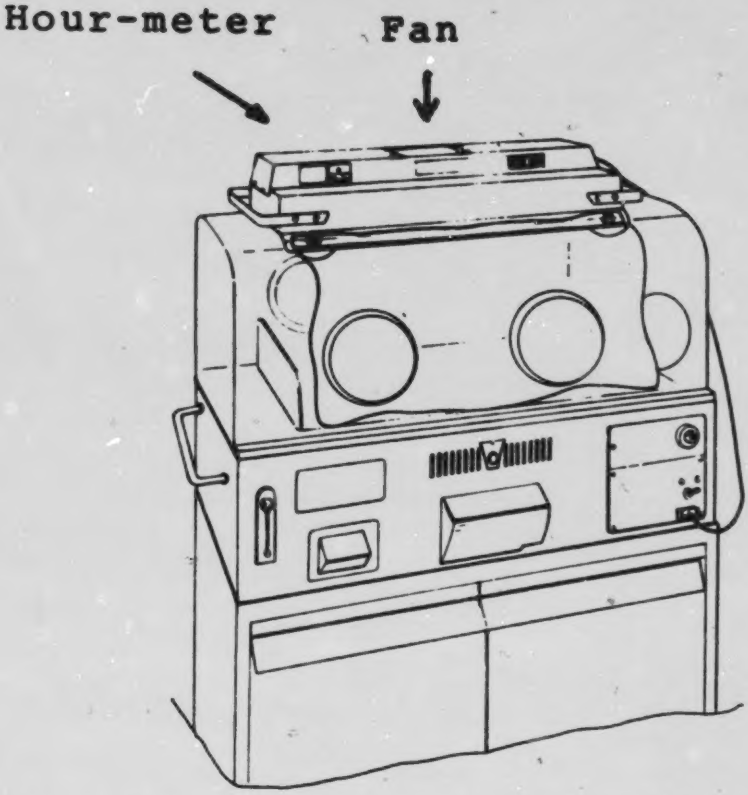

FIGURE 1. Schematic view of light chamber. The chamber is placed on the top of incubator. Note the fan and hour-meter.

ment of hyperbilirubinemic infants who are potential candidates of kernicterus. As a rule, this treatment is indicated when the serum bilirubin concentration exceeds 15–17 mg/100 ml in the full-term infant. In the low-birth-weight infant, phototherapy is started at the serum bilirubin level of 10–12 mg/100 ml. Phototherapy, however, is indicated at the lower bilirubin concentrations when the infant has idiopathic respiratory distress syndrome (IRDS), acidosis, hypoglycemia, extreme immaturity, hemolytic jaundice, and so forth, depending on the individual condition.

Growth in Early Infancy

The physical growth of infants who received phototherapy has been evaluated by several investigators.[4–7] Most of the studies previously re-

TABLE 2. *Energy decay of blue-white fluorescent lamps with use*

Duration of use (hours)	Percent decay[1]
100	6.5
1,000	10
3,000	16
5,000	24

[1] FL20 BW-NU.

TABLE 3. *Dose of light in incubator under phototherapy*

Location within incubator	Dose of light	
	Lux	Radiation energy (watts per square meter)
Center	5,520	28
Lateral	4,560	23
Top	3,050	16
End	3,110	16

Note.—Distance=30 centimeters; lamps=four 20-watt blue-white fluorescent tubes (FL20 BW-NU).

ported deal with the growth in late infancy and early childhood in infants who received phototherapy for the prophylaxis of hyperbilirubinemia. They include infants with several neonatal diseases that may affect the growth of infants. To evaluate the growth of phototreated infants in their early infancy, the growth of 44 low-birth-weight infants, who received

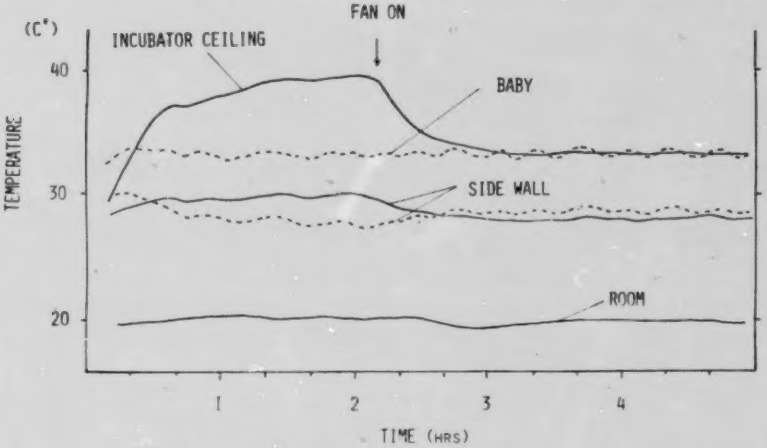

FIGURE 2. Ambient temperature during phototherapy. Ambient temperature is kept stable by the fan.

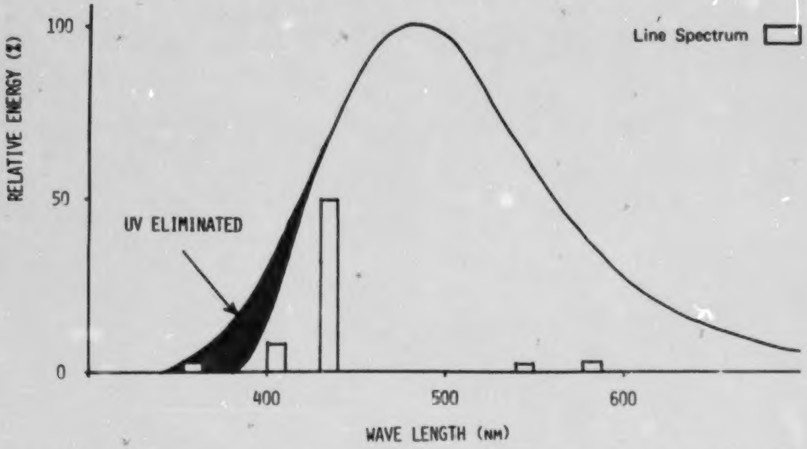

FIGURE 3. Radiation energy distribution of improved blue-white fluorescent lamp (Matsushita FL20 BW-NU). Energy from ultraviolet range (darkened area) is eliminated.

phototherapy but did not have any troubles other than hyperbilirubinemia, was compared with that of 53 other low-birth-weight infants without phototherapy whose neonatal courses were uneventful. Mean birth weights and gestational ages were similar in both groups (table 4). Body weights in early infancy were plotted on the standard growth curve corrected for gestational weeks according to the procedure described by Babson.[8] As shown in figures 4 and 5, one boy from each group fell below −2.0 standard deviations and one girl from each group also had a body weight below −2.0 standard deviations, but the majority exhibited body weight and growth

TABLE 4. *Subjects for survey on growth in early infancy*

Description	Treated	Nontreated
Total admission [1]	178	286
Sex:		
Male	84	136
Female	94	150
Study population [2]	44	53
Sex:		
Male	20	26
Female	24	27
Birth weight (grams)	1,898 ± 289	1,998 ± 238
Gestation (week:day)	34:1 ± 2:4	35:0 ± 2:4
Maximum total bilirubin (mg/100 ml)	14.3 ± 2.7	11.3 ± 2.9
Duration of phototherapy (hours)	75.8 ± 35.9	

[1] Total admissions of low-birth-weight infants within 72 hours after birth in the period of 1969–72.

[2] Normal low-birth-weight infants except for jaundice.

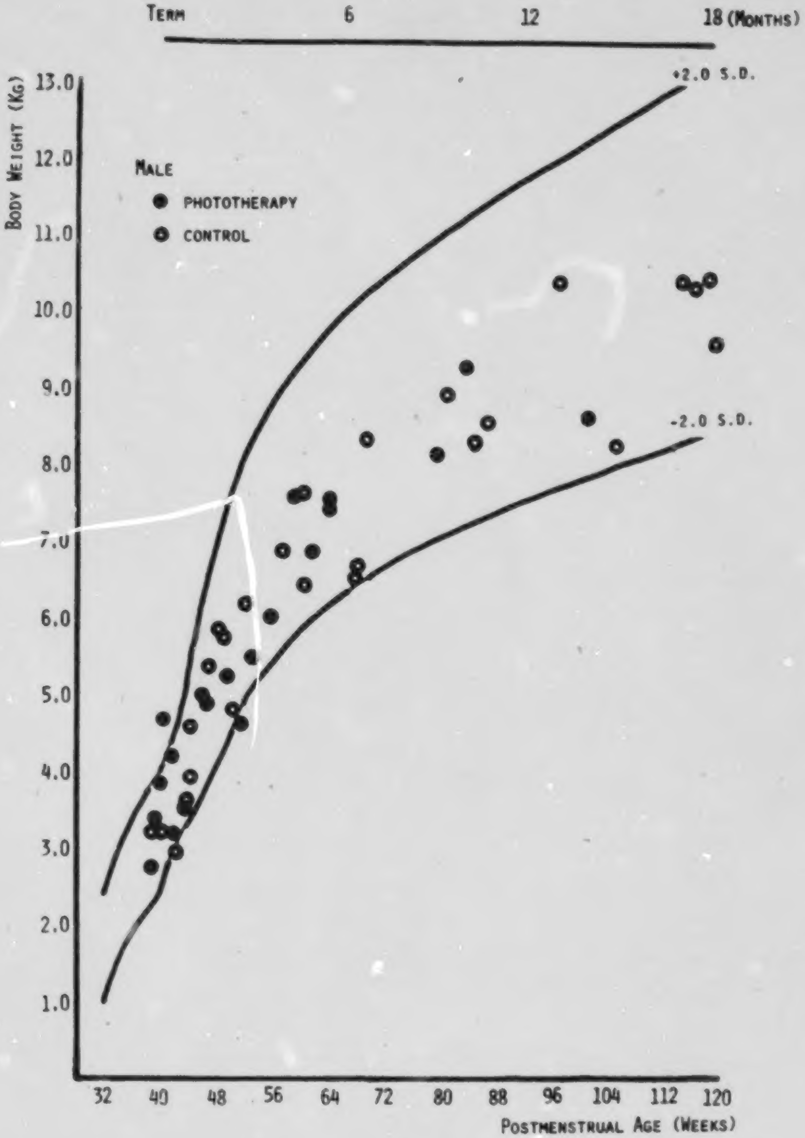

FIGURE 4. Body weight growth of boys in early infancy. Weights corrected for gestational weeks are plotted on the standard curve for Japanese boys.

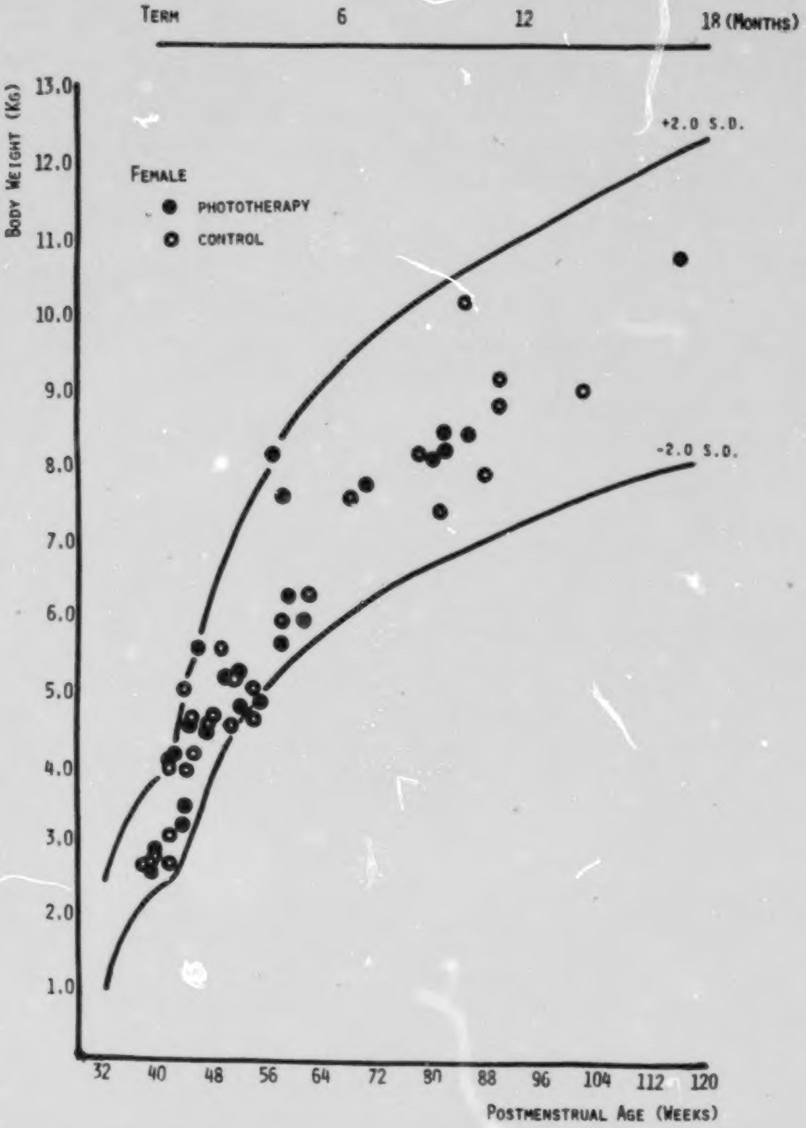

FIGURE 5. Body weight growth of girls in early infancy. Weights corrected by gestational weeks on the standard curve for Japanese girls.

within normal limits when the values plotted on the curve were corrected for gestational age. Recent controlled studies by Hodgman and her associates [7] have revealed that the growth of infants at 2 years is unaffected by the light. In their previous study,[5] however, growth of the treated infants was slightly worse when they were examined at the age of 8 to 16 months. As their study groups contained infants with various neonatal troubles, which themselves might affect the growth, further analyses on each infant might be indicated. Our present study, where factors possibly affecting subsequent growth were eliminated, demonstrates that the phototherapy per se does not show a deleterious effect on body weight or growth in early infancy.

Long-Term Followup Study

The true effect of light on subsequent growth and development may be accomplished by a followup study conducted on the infants who do not have any factors that may modify growth and development, with completely matched controls. Practically, however, phototherapy is generally applied for the treatment of hyperbilirubinemic infants with various neonatal troubles, and it is almost impossible to conduct an ideal followup study, especially in a referral center as ours. We have attempted, therefore, a controlled followup study with more practical samples.

In 1968, 44 infants were treated with phototherapy for hyperbilirubinemia. Twenty-two infants were born with birth weights over 2,500 grams (g) and 22 were low-birth-weight infants. Twenty-two other low-birth-weight infants admitted in the concurrent period were selected randomly among babies who were matched for birth weight and gestational age and who served as controls for light-treated low-birth-weight infants (table 5). A pair of twins were present; one in the control group and the other in the treated low-birth-weight group. The majority of infants were born in other institutions and referred to our neonatal care nursery for various neonatal problems. Both low-birth-weight groups contained the same number of IRDS of similar severity, but the matching for other major neonatal problems and pre- and perinatal histories was incomplete (table 6). In the light-treated groups, phototherapy was indicated solely for the treatment of hyperbilirubinemia and never for prophylaxis in which the irradiation is started on the first day. In five of the full-term and in three of the low-birth-weight infants, however, the treatment was indicated after exchange transfusion in an attempt to prevent the reelevation of serum bilirubin concentration (table 6).

No signs or symptoms suggesting kernicterus were detected in any of the infants. All infants in three groups were discharged from the nursery without detectable sequelae. Although the patient population in our hospital is highly mobile, careful and laborious tracings enabled us to contact all families of those infants 5 years after discharge (table 7). One infant in the

TABLE 5. *Neonatal characteristics of study population*

Characteristic	Phototherapy		Control
	>2,500 grams (*N*=22)	≤2,500 grams (*N*=22)	≤2,500 grams (*N*=22)
Birth weight (grams):			
Mean±*SD*	3,139±421	1,926±352	1,863±334
Gestation (week:day):			
Mean±*SD*	39.4± 1.5	34.1± 2.6	33.5± 2.6
Intrauterine growth (*SD*'s):			
>+1.5	3	0	0
+1.5~+0.5	5	2	1
+0.5~−0.5	6	7	8
−0.5~−1.5	6	7	7
<−1.5	2	6	6
Birth weight (grams):			
1,001–1,500		4	4
1,501–2,000		8	8
2,001–2,500		10	10
Gestation (week):			
26–29	0	2	3
30–33	0	9	10
34–37	5	11	7
38–42	17	0	2
Duration of phototherapy (hours):			
Mean±*SD*	57.6±35.8	74.8±35.1	
Maximum total bilirubin (mg/100 ml):			
Mean±*SD*	22.5± 5.2	16.8± 5.0	10.8± 2.7

Note.—*SD*=Standard deviation.

light-treated full-term group died at 13 months of age from pneumonia. Most of the infants returned for followup examination at the age of 5 years to 5 years 7 months. Some of them were visited at home and examined by one of us.

At the followup study, interval history, physical examination, neurologic examination, and developmental examination including the estimation of IQ were performed without prior knowledge of neonatal course. Weight, length, and head and chest circumferences were plotted on the standard growth curves for Japanese children.[9] IQ was estimated with the use of modified Binet test.[10] One infant from each group moved too far to return for followup, and a questionnaire was sent to the parents to ascertain growth and development. In that case, growth was evaluated on the measurements done by a home physician and development was evaluated by developmental quotient (DQ) determined on the answer from the parent.[11]

Table 8 presents the weights and heights at the time of followup examination. In the light-treated full-term group, none were below −2.0 standard deviations (*SD*). In the light-treated low-birth-weight group, one infant

TABLE 6. *Prenatal and neonatal histories of study population*

History	Phototherapy		Control
	>2,500 grams (*N*=22)	≤2,500 grams (*N*=22)	≤2,500 grams (*N*=22)
Prenatal:			
Positive	11	13	9
Negative	11	9	13
Asphyxia:			
(+)	4	6	3
(−)	18	16	19
Neonatal Problems:			
IRDS	0	3	3
Massive aspiration syndrome	0	1	0
Pneumomediastinum	1	0	0
Hemolytic anemia	1	0	0
Hypoglycemia	0	1	0
Hypocalcemia	0	1	0
Aseptic meningitis	0	1	0
Exchange transfusion	5	3	0

TABLE 7. *Number of infants in 5-year followup study*

Group description	Phototherapy		Control
	>2,500 grams	≤2,500 grams	≤2,500 grams
Death after discharge	1	0	0
Survived more than 5 years	21	22	22
5-year followup	21	22	22
Sex			
Male	12	9	10
Female	9	13	12
Followup examination	20	21	21
Questionnaire	1	1 (twin B)	1 (twin A)
Age (year:month):			
Mean ±*SD*	5:0.9±1.5	5:1.1±1.1	5:2.7±2.6

Note.—*SD*=Standard deviation.

fell below −2.0 *SD*, whereas three infants in the control group were below that level. Both low-birth-weight groups, treated or control, tended to have smaller body weights, but the difference between those two groups was not statistically significant.

TABLE 8. *Weight and height at followup*

Study infant	Phototherapy		Control
	>2,500 grams (*N*=21)	≦2,500 grams (*N*=22)	≦2,500 grams (*N*=22)
Weight[1] (kilograms):			
Mean±*SD*	16.7±1.5	15.9±2.3	15.1±1.9
SD:			
>+2.0	0	0	0
+2.0~+0.5	4	3	0
+0.5~-0.5	11	8 (1)	7 (2)
−0.5~−2.0	6	10 (5)	12 (3)
<−2.0	0	1	3 (1)
Height[2] (centimeters):			
Mean±*SD*	105.6±3.2	104.7±6.0	103.1±5.6
SD:			
>+2.0	0	0	0
+2.0~+0.5	5	6	1 (1)
+0.5~−0.5	10	9 (2)	10 (2)
+0.5~−2.0	6	6 (4)	9 (3)
<−2.0	0	1	2

Note.—Numbers in parentheses indicate small-for-dates infants.

[1] Japanese standard for 5–5.5 years (1970) for boys is 17.4±2.1 and for girls, 17.0±2.0.

[2] Japanese standard for 5–5.5 years (1970) for boys is 107.1±4.3 and for girls, 106.2±4.2.

Heights at the followup examination showed a similar pattern as weights did. Head and chest circumferences are summarized in table 9. The control group contained one child whose head circumference was below −2.0 SD. No child was observed with small head circumference in either light-treated group. No significant differences were found, however, between the treated and control groups. The control group also contained two children with small chest circumference, but again there were no significant differences between the treated and control groups.

Table 10 presents the IQ or DQ estimated at followup. No differences were found in the three groups, but two from each low-birth-weight group had borderline values. One child in the control group, indicated in the table, could not stay in the test room apart from his mother, and an accurate result could not be obtained. A score of 75 was given provisionally, judging from the general impression. Neurologic examination revealed no major problems in any of the three groups. Mild choreiform movements were detected in three children in the low-birth-weight group, two in the treated, and one in control groups. One infant in each low-birth-weight group was hyperkinetic. It was unlikely at that age, however, that those findings indicated signs for minimal brain disfunction.

TABLE 9. *Head and chest circumferences at followup*

Circumference	Phototherapy		Control
	>2,500 grams (*N*=21)	≤2,500 grams (*N*=22)	≤2,500 grams (*N*=22)
Head [1] (centimeters):			
Mean±*SD*	51.2±1.9	50.6±1.5	50.3±2.2
SD:			
>+2.0	2	0	0
+2.0~+0.5	5	9 (1)	10 (2)
+0.5~−0.5	12	10 (3)	6 (3)
−0.5~−2.0	2	3 (2)	5 (1)
<−2.0	0	0	1
Chest [2] (centimeters):			
Mean±*SD*	54.5±2.6	53.0±2.0	52.1±2.7
SD:			
>+2.0	1	0	0
+2.0~+0.5	4	3	1
+0.5~−0.5	11	11 (3)	10 (3)
−0.5~−2.0	5	8 (3)	9 (2)
<−2.0	0	0	2 (1)

Note.—Numbers in parentheses indicate small-for-dates infants.

[1] Japanese standard for 5–5.5 years (1970) for boys is 50.8±1.7 and for girls, 49.9±1.8.

[2] Japanese standard for 5–5.5 years (1970) for boys is 54.9±2.6 and for girls, 53.5±2.7.

Strabismus was found in three infants in the full-term group, one in the light-treated low-birth-weight group, and two in the control groups. Visual or hearing difficulties were not detected in any of the children.

Interval history revealed no major illness in any child after discharge from the nursery. Thus, growth and development of light-treated infants,

TABLE 10. *Developmental findings by number of infants at followup*

Development assessment	Phototherapy		Control
	>2,500 grams	≤2,500 grams	≤2,500 grams
Normal	21	20	20
Borderline	0	2	2
IQ:			
>121	1	2	1
120–80	19	18	19
79–70	0	1	0
<69	0	0	0
unavailable	0	0	1 (75?) [1]
DQ:			
Normal	1 (118)	0	0
Borderline		1 (75)	1 (73)
IQ	21(106.9±13.5) [2]	21(103.1±12.5)	20(104.1±11.1)

[1] Estimated score.

[2] Mean±standard deviation.

irrespective of birth weight, were within normal limits at the age of 5 years. No significant differences were observed in any respects of growth and development between the phototreated and control low-birth-weight groups. These results, obtained from this study of rather small numbers of infants, demonstrate that phototherapy does not affect growth and development even on a long-term basis.

BRONZE BABY SYNDROME

Kopelman, Brown, and Odell [12] reported a premature infant who developed an intense gray-brown discoloration of the skin, serum, and urine during phototherapy. A similar case was reported by Sharma et al.,[13] and this unusual condition has been called the bronze baby syndrome. This complication can be prevented in most of the cases by careful laboratory work to detect the presence of hemolysis or high direct reacting bilirubin concentration in the serum before starting phototherapy. During 5 years of phototherapy, however, we have observed 15 such infants, and the description of some characteristics observed in these infants may serve for the prevention of further occurrence in other institutions. The majority of cases were referred from other hospitals.

Analyses of these infants revealed that there were several common features or predisposing factors among the infants with this complication. Table 11 summarizes common features observed in these babies. All but two such infants had obstructive jaundice (direct reacting bilirubin over 3 mg/100 ml). More than half of the cases received exchange transfusion for hyperbilirubinemia or fresh blood transfusion for anemia. Hemorrhage was seen in nine cases. Hepatic damage was present in five babies. Two such infants received laparotomy for jejunal and ileal atresia. Spectral absorption curves were observed on the sera from six patients, showing that there were two major patterns. The one showed a Soret band at 405 nm and three small peaks at 460, 520, and 630 nm. The absorbance at 460 nm was attributed to bilirubin-albumin, and a Soret band with small peaks at 520 and 630 nm corresponded to the spectral absorption characteristic of methemalbumin [14] (figure 6). Electrophoresis indicated the benzidine-

TABLE 11. *Predisposing factors of bronze baby syndrome*

Features	Incidence (percent)
Obstructive jaundice	87
Exchange transfusion or blood transfusion	67
Hemorrhage	60
Hepatic damage	33
Infection	27
Hemolysis or erythroblastosis	20
Down's syndrome	20

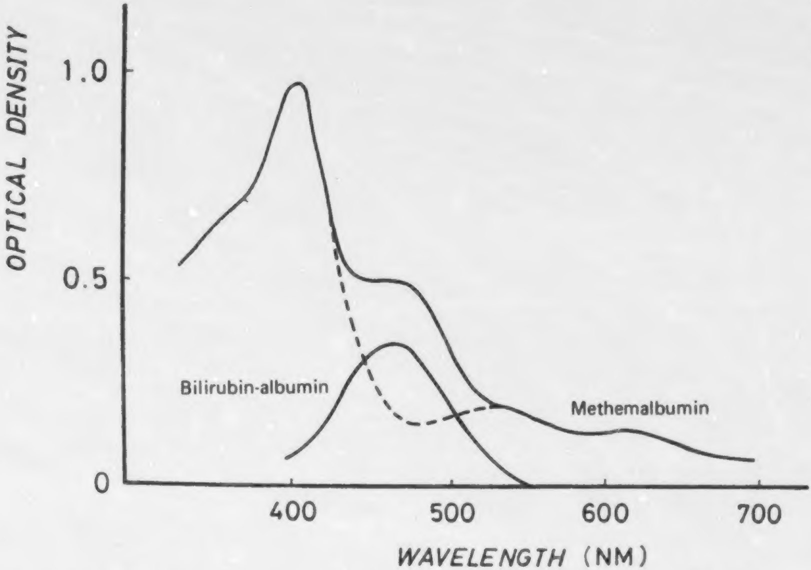

FIGURE 6. Absorption spectrum of serum from bronze baby syndrome. The curve resembles that of methemalbumin.

positive substance moving with albumin. The other group of sera had an absorption between 600–700 nm with the indistinct Soret band as a shoulder to the peak between 400 and 500. The absorbance between 600–700 nm suggested the presence of biliverdin in the sera (figure 7). In addition, our recent study with gel permeation chromatography, nuclear magnetic resonance, and mass spectrometry revealed the accumulation of bilifuscin in the serum of the baby with bronze baby syndrome.[15]

These observations suggest some possible mechanism in the development of the syndrome. As Ostrow [16] has reported, photodegradation products of bilirubin are rapidly excreted into the bile. In the infant with obstructive jaundice, photooxidation products are prevented from excreting into the bile. Thus the retention of photodecay substances is likely responsible for the unusual discoloration of skin, serum, and urine. Hemorrhage, especially the enclosed one such as intracranial bleeding, causes the increase of hemoglobin in plasma. In the newborn infant, haptoglobin and hemopexin, which are responsible for binding hemoglobin and hematin, respectively, are very low in concentration. Therefore, hematin tends to bind albumin and form methemalbumin. While in the intestinal hemorrhage, hemoglobin is decomposed to protoporphyrin with the aid of intestinal flora. The protoporphyrin, a known photosensitizer, may evoke hemolysis and in turn produce methemalbumin.

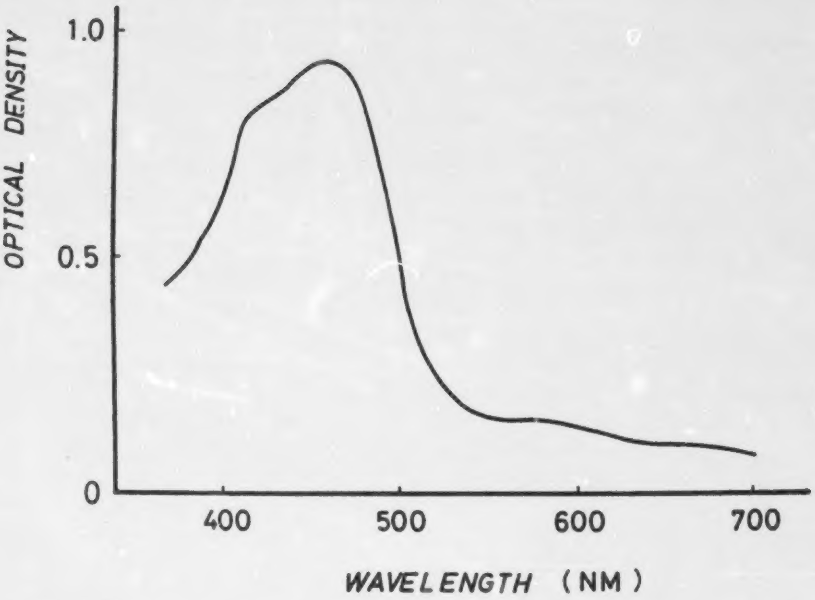

FIGURE 7. Absorption spectrum of serum from another group with bronze baby syndrome. The curve shows the pattern characteristic to biliverdin.

C-reactive protein, orosomucoid, and naptoglobin are acute phase reactants in the serum and are known to increase with infection.[7] Our bronze babies with septicemia, however, showed an elevation of all acute phase reactants except haptoglobin. This observation suggests the presence of hemolysis as well.

Of 15 bronze babies, death occurred in 4, all of whom died from the underlying diseases. They were autopsied and none of them had kernicterus. Among the remaining 11 infants, exchange transfusion reduced the symptoms in 6 cases, and others showed a gradual recovery by the cessation of phototherapy.

In five of our cases, unbound bilirubin was estimated with sephadex gel filtration technique. Values were elevated in all five to the range in danger of kernicterus. We have found that the sera with high direct reacting bilirubin concentration usually showed higher values of "unbound bilirubin" by gel filtration technique. Therefore, higher values in bronze babies do not necessarily mean the true increase in unbound bilirubin concentration. Further investigation is necessary to understand the events occurring under this unusual complication of phototherapy.

UNBOUND BILIRUBIN AND PHOTOTHERAPY

One of the potential hazards of phototherapy appears to be a possibility in the alteration of binding capacity of albumin to bilirubin. Odell, Brown, and Holtzman [18] have observed by equilibration of bilirubin bound to photooxidized albumin with suspensions of mitochondria that the bilirubin is more susceptible to displacement from albumin by salicylate and can be recovered in the mitochondria. No evidence has been shown to indicate whether photosensitized oxidation of albumin is likely to occur in infants under phototherapy.

We have observed the change of unbound bilirubin concentrations as well as salicylate saturation index in 33 infants treated with blue-white fluorescent light. As illustrated in figure 8, unbound bilirubin concentrations estimated by gel filtration technique and peroxidase method fell with the duration of phototherapy. Similarly, salicylate saturation index decreased during the course of phototherapy, suggesting that the serum albumin remained unaffected in vivo by the exposure to blue-white fluorescent light.

RIBOFLAVIN AND PHOTOTHERAPY

It has been speculated that the riboflavin may be affected by phototherapy. Ostrow [19] has quoted the observation by Slavin and Sisson that the serum riboflavin level in the newborn infant was lowered by the exposure to light. In order to determine the effect of light to riboflavin, its concentra-

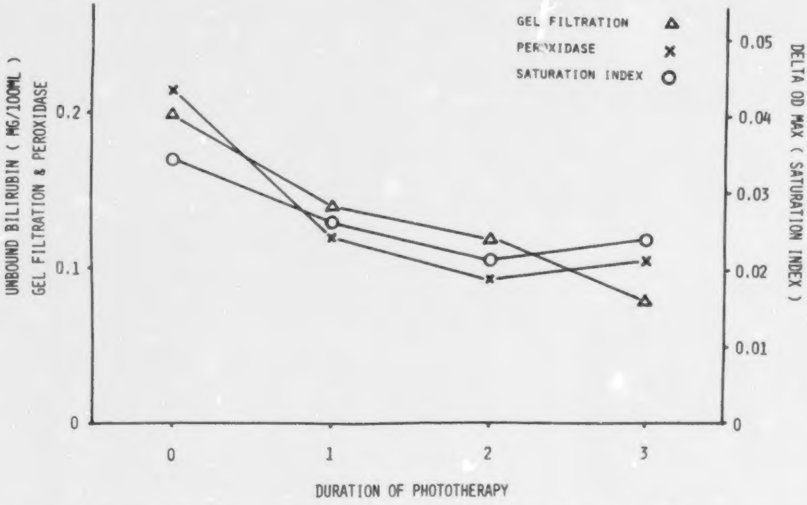

FIGURE 8. Effect of phototherapy on bilirubin albumin interaction. Unbound bilirubin concentrations as well as salicylate saturation index decrease by phototherapy.

tion in the whole blood was estimated by a microdetermination technique [20] in six infants before, at the cessation of, and 24 hours after phototherapy. As shown in table 12, riboflavin concentrations were mildly elevated in all but one during phototherapy. The mean concentration showed a small increase during phototherapy following a fall to the pretreatment level 24 hours after the treatment. Thus the whole blood riboflavin levels were not affected by phototherapy.

TABLE 12. *Concentration of whole blood riboflavin before and after phototherapy*

			Whole blood riboflavin (mg/100 ml)		
Birth weight (grams)	Age at treatment (day)	Duration of phototherapy (hours)	Before treatment	At cessation of treatment	24 hours after treatment
3,250	2	24	7.0	8.2	7.7
2,500	6	72	—	9.9	7.4
3,060	7	46	11.8	8.7	8.9
2,900	5	48	8.2	9.4	7.5
3,260	2	24	8.3	9.3	10.0
3,580	7	48	6.5	7.3	8.2
Mean			8.4	8.8	8.3

CONCLUSIONS

Five years' experience in phototherapy has been presented. Phototherapy was performed with the use of an improved light unit developed in our institution, solely for the treatment of hyperbilirubinemia, the incidence of which is higher in Japan than in Western countries. Followup studies of light-treated infants with appropriate controls showed no deleterious effects of light in growth and development both in early infancy and at 5 years of age. Neither unbound bilirubin nor riboflavin was affected by phototherapy, but unusual complication of phototherapy known as bronze baby syndrome was discovered in 15 infants, and some speculative considerations concerning its etiology was presented.

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Discussion

Dr. Behrman: I would like to open the discussion by asking Dr. Obes-Polleri if he would make a comment about any of the followups on the 5,000 cases that he has seen over the years. Do you have any information on that?

Dr. Obes-Polleri: I do not.

Dr. Hodgman: Dr. Obes-Polleri, you mentioned a long list of problems with phototherapy and the need for the careful use of eye bandages. I was curious as to why you felt that this was important?

Dr. Obes-Polleri: I do not believe that it is safe for the baby to be without an eye bandage. You have nothing to lose and, perhaps, a lot to gain. In 1,000 cases, however, I have never had a problem in the ophthalmology clinic. It is a precautionary measure.

Dr. Hodgman: You are using it to prevent the problem.

Dr. Obes-Polleri: I know of people here who do not use an eye bandage and have no problem.

Dr. Indyk: Dr. Obes Polleri, you implied that a standardized unit was not necessary. I do not think that one can build a phototherapy unit and say that after 100 hours of use, it is going to operate in the way that it was operating before.

Dr. Ostrow: These papers are beautifully organized, careful, and thorough studies. I think that we could probably conclude that there is no gross evidence of any serious damage. This is a question that was not answered previously. We cannot conclude, however, that minor or subtle differences do not occur in a small number of patients—the experimental groups are too small to get statistically significant differences. If the differences are small, let us say an increase from 1 to 2 percent, or a low IQ, up to 6 percent of subjects, hundreds of patients are needed to demonstrate that sort of change. Nonetheless, these studies are and will be used as models for some time. Of course, a big problem is how do you justifiably withold this treatment with the data we have at present?

Dr. Gartner: The critical issue as I see it in these studies is not just to show there is no difference between the control and treated groups, but to demonstrate the effectiveness of phototherapy by a significant improvement in the neurological performance of the phototherapy-treated infant in comparison with the control group. These studies do not have sufficient numbers of subjects to expect to see significant differences. The same is true, however, of the pilot study report that we will present this afternoon. We have to assume from other studies that at least a portion of the low-birth-weight population is at risk from detrimental effects of hyperbilirubinemia. I think you must include within your study population patients who are in that category.

Dr. Odell: I would like to ask Dr. Ogawa a question about his study. I know of six babies in which the direct reacting bilirubin was not elevated at the onset of phototherapy, but it became elevated after it was initiated. Also at that time, some of the transaminases went up.

Dr. Ogawa: Most of the babies referred from other hospitals had a high bilirubin level when they arrived at our hospital. So we did not know the precise data before.

Dr. Kapitulnik: We have seen a phenomenon in the babies—you have seen that there is a decrease in the amount of bilirubin, but I would like to ask you if it is related to an actual decrease or a lowering in the concentration? What do you think of the cases in which there is no decrease in the concentration in the first 24 hours? I would like to go into the reason why bilirubin is not decreasing.

Dr. Ogawa: I do not know because we have not analyzed it in such a way.

Dr. Odell: There is some data on that. There is no uniform alteration in free bilirubin that is detected in gel and after exchange transfusion. In the six cases that I just went over before I came down here, I was surprised that there was not a uniform decrease in that fraction.

Dr. Schmid: I have a couple of questions. First, how did you select the patients who went into the study? Was this random selection or was there a selection mechanism?

Dr. Ogawa: As to the long-term followup, we had only 44 cases.

Dr. Schmid: When you decided that they should get light or be controls, how did you select the patients?

Dr. Ogawa: Five years ago among the babies in our nursery, only 44 babies developed hyperbilirubinemia so we gave phototherapy to those.

Dr. Brown: What is hyperbilirubinemia in Japan?

Dr. Ogawa: We usually start phototherapy in full-term infants if the infants show the serum bilirubin over 15 to 17 milligrams percent. In the low-birth-weight infant, it would be 10 to 12 milligrams percent.

Dr. Schmid: All these infants went into the phototherapy study. How did you select your controls?

Dr. Ogawa: We selected controls from the nontreated infants and we tried to match gestational age and birth weight.

Dr. Schmid: You suggested this morning that you selected two groups of infants and those two groups should have the same level of bilirubin, should they not?

Dr. Johnson: If I remember the figures correctly, the controls were 11 milligrams percent and the treated were 14 milligrams percent. If you were to see any damage, it should be in the treated group, which had the higher serum bilirubin concentration.

Dr. Schmid: I have another question. I did not understand the bronze baby study. You mentioned two pigments.

Dr. Ogawa: We had one case where we analyzed the serum.

Dr. Schmid: What was the peak that eluted with spectral absorption at 405 nanometers?

Dr. Lowe: I think he said that the study showed that there is no long-term, prejudicial effect on babies from phototherapy. I think that it is reasonable to raise the question of whether the method of analysis of height and weight at 2 years or 5 years, as presented actually, is appropriate?

Dr. Anderson: I wondered whether the population at 2 years was distributed quite differently. I am suggesting that you had better look at the distribution of the patients in different categories of height and weight. I think that you will find that there are differences.

Dr. Hodgman: For reasons that I cannot explain we have a different growth pattern than this study.

Dr. Ostrow: I wanted to comment on the bronze baby situation. First, the serum of some patients who have cirrhosis contains a significant proportion of unconjugated bilirubin. Second, if the flow of bile is obstructed in the Gunn rats during phototherapy, the serum becomes bronzed and the urine becomes bronze in appearance, for reasons that I do not understand.

Dr. Brown: On this point, if we could discuss the bronze baby after you have presented your data about the nature of altered bilirubin, we might get more to the point, for if what is happening is that the bilirubin is altered in such a way that the liver recognizes it as something that is excretable, even though it appears to be unconjugated bilirubin when analyzed, then a state of biliary obstruction would lead to accumulation of a pigment in the serum that would not have been recognized before.

Dr. Behrman: Is it the general consensus here that we have laid to rest substantially the question of obvious effects on growth?

Dr. Lowe: As I recall, Dr. Ogawa, Dr. Johnson, and Dr. Hodgman all treated their infants over a period of what seemed to be an average of 2 to 3½ days; on the other hand, Dr. Ploussard treated for an average of 5 days.

I am wondering whether, as a very tentative kind of unsubstantiated hypothesis, it would be worth looking into the question of whether the extended phototherapy may not in some way photodegrade some essential component of growth and that the short-term phototherapy and the short-term stops in growth that were reported were caught up again by the first year. I am posing this as a possible explanation.

Dr. Hodgman: Our babies were treated for 5 days. In one group, the treatment was given continuously for 5 days; the other group was given treatment intermittently for 5 days.

Dr. Gartner: On the matter of the subtle versus the gross in followup studies, would someone care to speculate on what sort of functions one should examine?

Dr. Schmid: Dr. Ogawa's study is the first one in which the therapy is being applied without the infants becoming exposed to a heat stress. They had a fan to keep the infant cool. His was the first data that seem to show that there was no growth-retarding effect, even though I would be interested in the studies that Dr. Hodgman and other people have done with regard to heat stress.

I would like to propose that this is related to water loss from the effect of heat stress, which is subsequently recovered.

Dr. Behrman: Any other comments?

Dr. Hodgman: The major question that has been raised thus far has been about the effect of bilirubin on long-term development. We have to look at phototherapy-treated babies, but I do not think that we can do it with our population.

Dr. Johnson: We do not really know what light will do, and that is the question that we are trying to answer.

Dr. Behrman: Are there any other comments?

Dr. Lucey: An important fact that we have chosen to ignore after a few weeks in the nursery is the home and family—control here is difficult. We have had groups present data that I am sure, had different growth patterns—Spanish Americans and blacks. You had heard about the condition of temperature control, which has not been mentioned, and its effect on head growth. The basis of handling and mothering has been ignored. I am quite sure that not only genetic potential but the home conditions are important.

Growth patterns among premature infants have been reported in which no light was used. There is one study showing that there is a different rate of weight gain and growth pattern for different types of premature, small-for-gestational-age, and normal premature infants. Nobody has mentioned any possibility regarding the drugs that the mother may have taken. I believe that we can combine all these things and discourage the giving of a simple yes or no answer on the basis of what we know at this time. You have not yet come up with any proper definition to satisfy my conditions for a control group.

Dr. Gartner: When the bilirubin level is the criteria for admission to a phototherapy study, you cannot have suitable controls. Prophylactic control studies overcome this objection. Sufficiently large study populations also randomize for other possible variations due to child-rearing practices, drugs, etc. As in any developmental study, data on serial growth, development, social and family status, and drugs must be kept and compared.

Dr. Behrman: One last comment.

Dr. Lowe: The view of a statistician is that lack of significance does not prove that the effect was not there, and it may only prove that the sample was too small. I do not think that we should lose sight of that fact.

Dr. Behrman: That is a good comment to end on.

Prophylactic Use of Phototherapy in Low-Birth-Weight Infants: Experience With a Controlled Clinical Trial Pilot Study

Lawrence M. Gartner, Ilana Zarafu, Kwang Sun Lee,
and Arthur Eidelman

Previous controlled clinical studies of the effectiveness of phototherapy in the treatment of neonatal hyperbilirubinemia have focused largely on serum bilirubin concentrations and on short-term effects of phototherapy on weight gain, linear and head growth, stool patterns, insensible water loss, and hematologic status.[1-10] Long-term controlled studies on the efficacy of phototherapy in reducing the incidence and severity of bilirubin encephalopathy and its possible deleterious effects on growth, endocrine maturation, or neurobehavioral development have not been reported.

Under the direction of the Division of Neonatology of the Albert Einstein College of Medicine, a pilot study was undertaken in 1971 at the Bronx Municipal Hospital Center (BMHC) in order to evaluate an experimental protocol to measure both short-term and long-term effects of phototherapy.

A sufficient number of infants were studied to test the practicality of the procedures, but no attempt was made to study a sufficiently large population to insure that statistically significant conclusions could be drawn. The pilot study was limited to the neonatal period. Long-term testing for neurologic, behavioral, sensory, and endocrine functions was deferred to a later time.

Three basic issues in the experimental design were initially considered. The first was the proper selection of infants and their assignment to appropriate categories to insure evenly matched test and control populations. The second was the need to standardize the therapeutic modality, that is, the light source, the time of initiation, and the duration of therapy. The third issue was the delineation of clinical and laboratory examinations capable of detecting differences between test and control groups.

This report will focus primarily on the first issue—the selection of an appropriate population for study and the difficulties of interpreting data when unexpected random differences between test and control groups emerge.

METHOD

All infants admitted to the BMHC Neonatal Center who weighed less than 2,500 grams were considered to be candidates for inclusion in the study. Only when informed consent was obtained from a parent was random assignment made to phototherapy or control group by selection of a sealed envelope containing the group designation. Matching was facilitated by randomizing infants into cells divided by sex, race, and 250-gram birth-weight increments. Only 1 out of the 47 families contacted refused permission for inclusion of the infant in the study.

Entry into the study was at the same time of day, 10 a.m., regardless of time of birth, providing that the age at time of entry was more than 12 hours and less than 36 hours. The mean time for entry was 24 hours. All blood, both preentry and followup, was drawn at the same time of day for all infants, so that results could be related to known finite periods of phototherapy exposure and to minimize any possible effects of circadian rhythm. The phototherapy period lasted for 6 days in all treated infants, and identical laboratory and clinical studies were performed in control and treated infants.

Phototherapy was delivered by a bank of eight 20-watt fluorescent General Electric Daylight lamps in an Air Shields fixture. All infants were housed in either patient servo-controlled or air temperature thermostat-controlled incubators (Isolette). Light intensity was monitored intermittently with a simple photometer supplied by Westinghouse Electric.[a] The photometer recorded the light emitted only in the wavelengths between 400–500 nanometers (nm). Lamps were replaced when the output decreased by more than 10 percent. Using a calibrated American Ultraviolet (PT 100c) photometer,[b] mean light energy intensity (± standard deviation) under the phototherapy lamps in the 380 to 489 nm range measured 403.1 ± 13.2 microwatts per square centimeter ($\mu W/cm^2$) in the center of the Isolette at the level of the infant's abdomen 12 inches below the lamp surface. Mean ambient light energy in the room where the control infants were housed measured 3.63 $\mu W/cm^2$ over the same wavelength range and ranged from 0.2 to 12.1 $\mu W/cm^2$ depending on window illumination. Thus, ambient light energy in the wavelengths of concern averaged only 1 percent of phototherapy illumination, and never exceeded 3 percent. Control infants were kept in rooms separate from test infants to eliminate exposure to scatter light from the phototherapy units. Phototherapy was continuous for 6 complete days except for short periods when blood was drawn or eye patches changed, every 12 hours.

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[a] Courtesy of Dr. Richard Corth, Westinghouse Electric.

[b] On loan from International Light, Inc., Newburyport, Mass.

Exchange transfusions were performed in all infants whose total serum bilirubins rose to levels indicated in table 1. The scale was based on birth weight and health status. The same criteria were used for both phototherapy and control infants.

Total and direct reacting serum bilirubin concentrations were determined daily by the same technician in the research laboratory, using a micromodification of the Evelyn-Malloy technique.[11] Reserve albumin bilirubin binding capacity was determined daily by a fluorescent dye technique, previously described.[12] Serum albumin concentrations were determined by the Mancini radial immunodiffusion method.[13] All methods were carefully calibrated against Versatol standards.

TABLE 1. *Criteria for exchange transfusion*

Birth weight (in grams)	Total serum bilirubin (milligrams per 100 milliliters)	
	A[1]	B[2]
<1,250	13	10
1,250–1,499	15	13
1,500–2,000	17	15
2,001–2,500	18	17
>2,500	20	18

[1] A = normal infant.

[2] B = infants with demonstrated hemolytic disease, prior hypoxia, acidosis, hypoglycemia, hypoalbuminemia, or hypothermia.

RESULTS

Gestational Age and Birth Weight

Twenty-two infants were entered into the phototherapy treatment group, 24 infants served as controls. The mean birth weight of the phototherapy group was 1,557±351 grams compared to a mean of 1,764±376 grams in the control group (table 2). This difference is not statistically significant ($p>0.05$). Gestational age, sex, and racial distribution of the two groups are also not significantly different (table 2).

Frequency distribution analysis of the two groups reveals that the phototherapy group had an increased number of infants with birth weights 1,500 grams and under (figure 1). These differences in distribution are not significant (chi-square test, $p>0.05$). Frequency distribution of birth weight for gestational age by percentile groupings according to Lubchenko[14] yields a different result, however, with the phototherapy group having a

TABLE 2. *Characteristics of patients in control and phototherapy groups*

Characteristic	Control	Phototherapy	*p*
Total number of patients	24	11	
Birth weight (grams) (Mean±*SD*[1])	1764±376	1557±351	>0.05
Gestational age (weeks) (Mean±*SD*)	35.0±2.5	34.4±2.2	>0.05
Male	12	12	>0.05
Female	12	10	
White	10	10	>0.05
Black	14	12	

[1] *SD* = standard deviation.

significantly ($p<0.05$) greater number of infants with birth weights in the 10th percentile and under as compared with control group (figure 1). Thus it would appear that despite random allocation of the population, a disproportionate percentage of small-for-dates infants entered the light group. Had analysis of the groups been limited to comparison of birth weights and gestational ages alone, it would have appeared that the two groups were statistically indistinguishable.

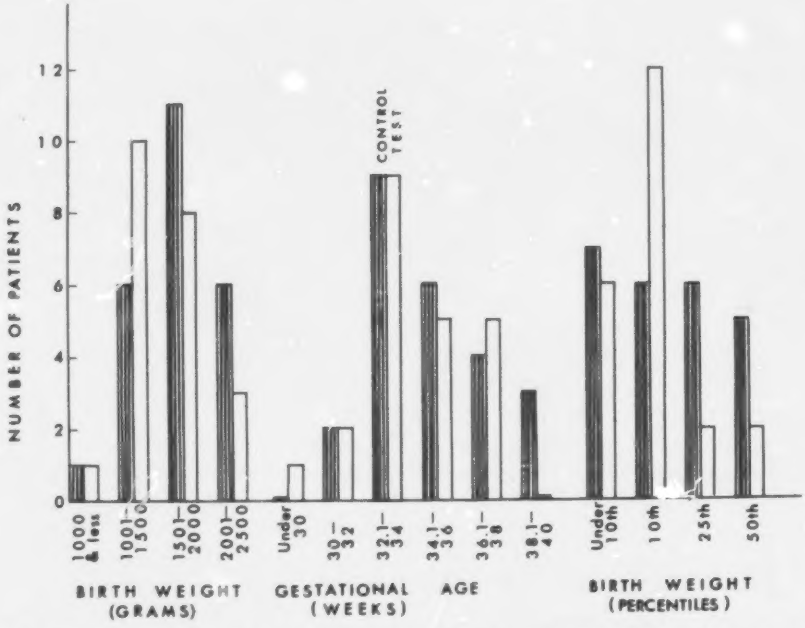

FIGURE 1. Frequency distribution of control and phototherapy (test) infants by birth weight, gestational age, and birth-weight percentiles for gestational age.

Clinical Status

The small number of infants in both groups and the marked heterogeneity in maternal history, intrapartum care, and neonatal course precluded any statistical analysis of these variables. One infant from each group, in each case weighing less than 1,000 grams, died with severe respiratory distress syndrome.

Stool frequency increased significantly in the phototherapy group only on day 3 of treatment ($p<0.05$). On days 4, 5, and 6, phototherapy infants also demonstrated increased numbers of stool, but differences were not significant ($p>0.05$). After discontinuance of phototherapy, stool frequency was identical in both groups.

Hematologic Status

One infant in each group had Coombs positive ABO incompatibility. No Rh hemolytic disease was observed. Prior to onset of therapy, hematocrits of the phototherapy and control groups were not significantly different ($p>0.05$). During phototherapy and until the 60th day of life, mean daily hematocrits of the phototherapy group declined at a slightly increased rate as compared to the controls, but the differences were not significant.

Vital Signs

No difference was noted between the phototherapy and control groups in respiratory rate, pulse rate, or axillary body temperature during the 6 days of therapy or in a followup period of 5 additional days.

Bilirubin Concentrations

The mean total serum bilirubin concentration in the control group reached a maximum of 8.3 milligrams percent (mg%) on day 4, while the maximum mean value in the phototherapy group was 5.2 mg% on days 2 and 4 (figure 2). After the fourth day of life, serum bilirubin concentrations declined in both the phototherapy and control groups, and by day 8 and thereafter they were the same in both. The differences between mean daily bilirubin concentrations in the phototherapy and control groups were significant on days 3 through 7 ($p<0.01$). In all 22 phototherapy patients, serum bilirubin concentrations were effectively reduced or maintained at concentrations below 8 mg% within 48 hours of institution of therapy regardless of clinical status, skin color, or gestational age.

The mean *peak* total bilirubin concentration, regardless of age of infant was 9.75±4.59 mg% in the control group, while in the phototherapy group, the mean peak value was 6.54±1.89. This difference between the two groups is significant ($p<0.05$).

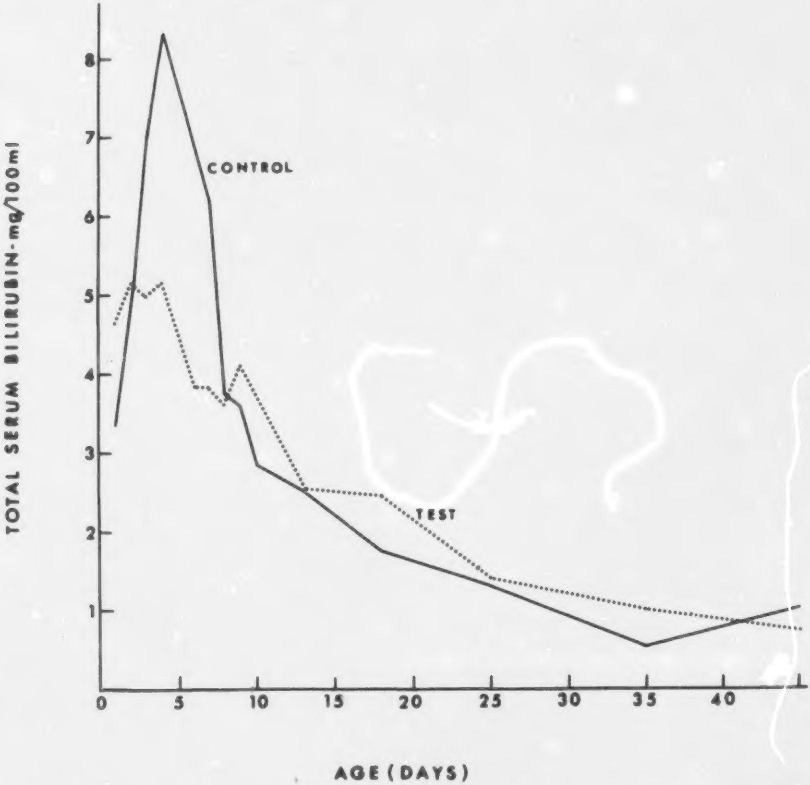

FIGURE 2. Mean daily total serum bilirubin concentrations in milligrams per 100 milliliters (mg/100 ml) of control (solid line) and phototherapy (test) (dotted line) infants during the first 45 days of life. Differences between groups are significant only on days 3 through 7 ($p<0.01$).

Analysis of serum bilirubin concentrations of individual infants revealed that there was a subpopulation of infants, three in the control group and one in the phototherapy group, who had unusually low maximal serum bilirubin concentrations ranging from 1.6 to 2.1 mg% (table 3). All of these infants were small for gestational age. It should be noted, however, that not all infants who were less than the 10th percentile for weight demonstrated this low serum bilirubin pattern. Three other infants in the control group and five in the phototherapy group who were under the 10th percentile for weight had the more typical pattern of hyperbilirubinemia.

No infants developed any abnormal pigmentation or bronzing of the skin.

TABLE 3. *Characteristics of infants with minimal neonatal hyperbilirubinemia*

Patient	Birth weight (grams)	Gestational age			Peak total serum bilirubin (milligrams per 100 milliliters)
		History	Physical	Neuro [1]	
Control:					
R	1800	41 (<10)	38 (<10)	37 (<10)	1.6
H	2350	42 (<10)	42 (<10)	38 (10)	1.8
M	2000	?	39 (<10)	35 (25)	1.9
Test:					
J	1420	?	37 (<10)	36 (<10)	2.1

Note.—Numbers in parentheses indicate birth weight percentile.

[1] Neurobehavioral development.

Exchange Transfusions

Four infants in the control group but none in the phototherapy group received exchange transfusions ($p<0.05$). Three of the infants required only one exchange but the fourth required five. In all of these cases, hyperbilirubinemia was attributed to immaturity in the absence of any other demonstrated cause. No morbidity or mortality relating to the exchange was observed.

Bilirubin Binding

Albumin bilirubin binding reserve capacity varied inversely with serum bilirubin concentrations. No significant differences were noted between the test and control groups over a range of bilirubin concentrations. Serum albumin levels were identical in both groups prior to onset of therapy, and although mean concentrations in the test group were higher during and after the phototherapy period (days 2–30), the differences were not significant ($p>0.05$).

Growth

Mean head circumference and body length at birth were smaller in the phototherapy infants as compared with controls and remained consistently smaller throughout the first 4 weeks of life whether compared on the basis of absolute measurements or as percent change from birth (tables 4 and 5). These differences were not significant, however, and probably represent the previously noted differences between the two groups in fetal growth patterns, with the phototherapy group having a significantly greater fre-

TABLE 4. *Mean head circumferences*

Age	Centimeters		Percent change from birth	
	Control	Phototherapy	Control	Phototherapy
Birth	29.77 ± 1.94	29.10 ± 1.85	—	—
Week 1	29.90 ± 2.05	29.31 ± 2.46	+0.81 ± 2.26	+0.93 ± 2.62
Week 2	31.03 ± 1.25	30.26 ± 1.67	+4.50 ± 1.65	+3.05 ± 2.96
Week 3	31.88 ± 1.97	30.75 ± 1.13	+7.67 ± 3.33	+5.15 ± 3.51
Week 4	32.30 ± 1.57	31.94 ± 1.21	+10.33 ± 4.12	+7.56 ± 2.60

Note—Differences between control and phototherapy groups were not significant ($p > 0.05$).

TABLE 5. *Mean body length*

Age	Centimeters		Percent change from birth	
	Control	Phototherapy	Control	Phototherapy
Birth	42.76 ± 3.01	41.50 ± 3.23	—	—
Week 1	43.32 ± 3.01	41.80 ± 3.10	+1.27 ± 1.61	+1.73 ± 2.49
Week 2	44.72 ± 2.25	42.86 ± 3.39	+3.39 ± 2.43	+3.79 ± 2.64
Week 3	46.25 ± 4.29	43.60 ± 2.30	+8.50 ± 5.45	+6.80 ± 4.02
Week 4	45.90 ± 2.78	44.33 ± 3.09	+6.60 ± 3.53	+7.89 ± 3.33

Note.—Differences between control and phototherapy groups were not significant ($p > 0.05$).

quency of small-for-dates infants despite no significant differences in mean birth weight and gestational age.

As previously noted, the phototherapy group had a preponderance of lower birth weight, small-for-gestational-age infants compared to the controls. As a result, intravenous therapy was more frequently instituted in the phototherapy group, and they consistently had greater fluid intake, ranging from 6–14 cc per day more than controls during the first 2 weeks of life (figure 3). These differences were not statistically significant, however. Mean caloric intake during this period was identical in both groups.

Changes of weight were expressed as percentage changes from birth weight. A significant difference was noted between the test and control groups on days 3–7 of life ($p<0.01$), with the infants in the phototherapy group losing proportionally less weight (figure 4). Beyond the first week of life, no consistent differences were noted. This observation is contrary to expectation and probably reflects both the increased fluid intake of the phototherapy group and the large proportion of small-for-dates infants, some of whom had little or no initial weight loss.

DISCUSSION

The results of this pilot study clearly demonstrate the difficulty in designing a study to test the effect of phototherapy on a population of low-birth-weight infants. Despite careful randomization of the infants into preset cells by sex, race, and birth weight, analysis of the population revealed poor

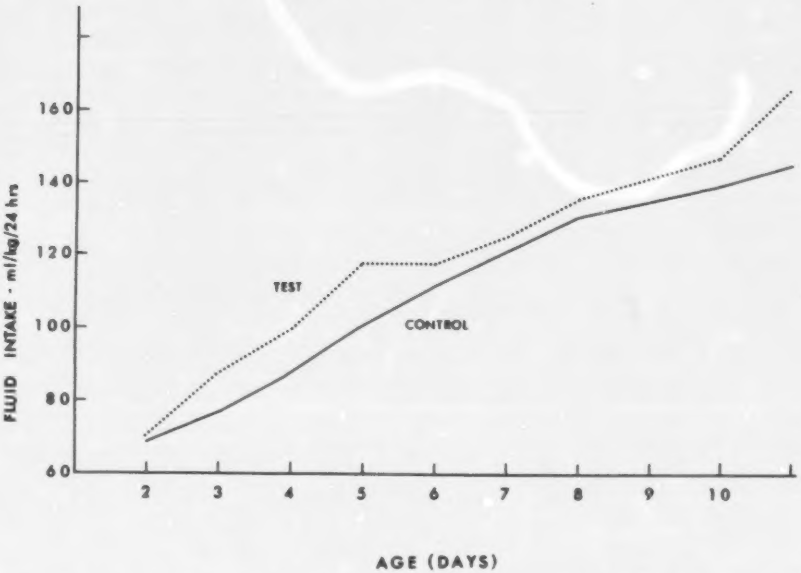

FIGURE 3. Mean daily fluid intake in milliliters per kilogram per 24 hours (ml/kg/24 hrs) of control (solid line) and phototherapy (test) (dotted line) infants during the 2d to 11th days of life. Difference between groups were not significant (p>0.05).

matching for intrauterine growth patterns. Mean birth weights and gestational ages were not significantly different, but the number of small-for-dates infants in the phototherapy group was significantly greater. Short-term evaluation of the effect of phototherapy on growth and bilirubin metabolism were clearly affected by the accidental poor matching of the populations studied. Some, but not all, of the small-for-gestational-age infants in the control group did not develop any hyperbilirubinemia, minimizing the apparent effectiveness of phototherapy in reducing serum bilirubin concentrations.

Analysis for weight patterns and fluid intakes was complicated by the fact that small-for-gestational-age infants received more intravenous therapy and lost somewhat less weight as a result. In addition, their weight-loss pattern may have been affected by their possibly decreased body water content. This reduced weight loss in the phototherapy group is clearly contrary to previous reports[3] of increased fluid loss under the phototherapy lights as a result of increased stool and insensible water excretion. These differences in the two populations might also influence long-term outcome measures and must be guarded against in future large-scale investigations.

The study design employed a prophylactic mode of phototherapy in order to provide better matching of the treated and control groups and to

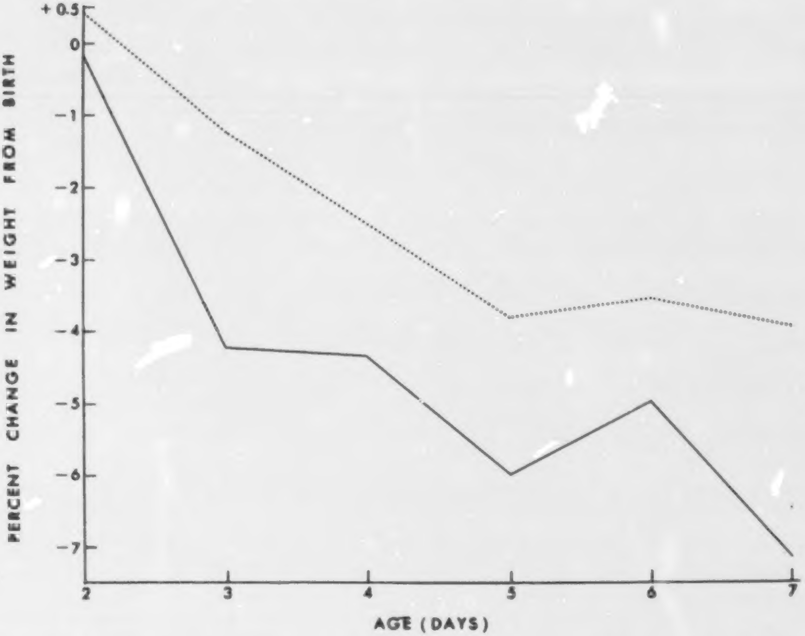

FIGURE 4. Mean percent change in weight from birth in the control (solid line) and phototherapy (dotted line) groups during the second to seventh days of life. Differences between groups on the third through seventh days of life were significant ($p<0.01$).

include those low-birth-weight infants who develop kernicterus despite low serum bilirubin concentrations.[15,16] A disadvantage of this type of selection is apparent from the observation that 3 of 24 control infants had maximal serum bilirubin concentrations of less than 2.0 milligrams per 100 milliliters and clearly were not at risk.

This limited experience with a small study population illustrates many of the potential pitfalls of a controlled clinical trial despite randomization of the subjects. Had the groups numbered in the hundreds, it is likely that these differences would have been minimized, but it is essential that analysis of data include critical appraisals of the groups for specific factors of difference that are not usually considered, such as fetal growth patterns, differences in weight distributions despite similar mean weights, and disproportionate distributions of subpopulations, which will skew results. Computerized techniques will facilitate the analysis of data with greater likelihood that finer discriminations among variables will be detected.

The small size of the pilot study population precludes the drawing of any conclusions, and the temptation to do so has been resisted by the authors. The results reported only indicate possible areas for further examination in larger studies and in some cases are in agreement with previously reported findings by others.

Experience with this pilot study has been extremely useful in developing a larger collaborative study that will seek to answer the more subtle long-term questions regarding effectiveness of phototherapy in the prevention of kernicterus and possible long-term toxic effects of the use of high-intensity visible light during the early newborn period. The ultimate objective in this type of study requires long periods of followup and detailed neurologic and behavioral evaluations. These evaluation procedures are currently under development.

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A Simple Method of Phototherapy and Thermotherapy[a]

K. L. Tan

Phototherapy has now been established as an effective means of lowering bilirubin levels in newborn infants, especially prematures, since Cremer, Perryman, and Richards[1] first demonstrated its effectiveness in 1958. It has been reported to reduce the incidence of hyperbilirubinemia from 22 percent to 1.6 percent.[2]

Radiant heat as a means of keeping newborn prematures warm has been used effectively in the Kandang Kerbau Hospital, Singapore, for over 5 years because of the lack of sufficient incubators to cater for over 1,500 low-birth-weight infants that are being delivered annually. This form of "thermotherapy" provided by incandescent lamps has been found to be very convenient, comparatively inexpensive, and very efficient providing instant heat for the infants. Nursing care of the infants has also been found to be less complicated and easier. No untoward effects have been encountered in these infants. Since phototherapy has been demonstrated to effectively reduce the incidence of hyperbilirubinemia, it was thought worthwhile to explore the feasibility of using incandescent lamps of suitable wavelength (for phototherapy) to provide not only thermotherapy but also phototherapy.

MATERIAL AND METHOD

Infants admitted to the premature nursery in the Kandang Kerbau Hospital, Singapore, were allocated at random to either the conventional incubators or Plexiglas chambers illuminated from within by blue lamps. In all of the infants, the following studies were performed at admission: blood typing, direct Coombs test, hemoglobin, blood picture, reticulocyte count, and glucose 6-phosphate dehydrogenase activity. The mothers' bloods were also typed and antibody studies performed. Infants with evidence of ABO or rhesus hemolytic disease, or glucose 6-phosphate dehydrogenase deficiency were excluded from the study. Every infant was given an injection of vitamin K_1 (1 milligram intramuscularly) on admission. To allow for valid comparisons to be made, only Chinese infants were studied.

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[a] I would like to thank Professor Wong Hock Boon for encouragement and advice, C. Y. Tye for statistical evaluation of the results, the Medical Superintendent of the Kandang Kerbau Hospital, Singapore, for permission to perform this study, the nursing personnel for their enthusiastic help and cooperation, and L. S. Tan for help with the figures. I am especially grateful to Dr. Kuang Lee Tan for performing the light energy and illumination measurements.

Capillary samples were collected in heparinized capillary tubes every morning (8 to 8:15) for bilirubin estimation from each infant for 1 week. In those with bilirubin levels above 10 milligrams (mg) per 100 milliliters (ml) at the end of the week, such determinations were continued until the level fell to 10 mg or lower. Plasma bilirubin was determined by the AO Bilirubinometer (American Optical Corporation) in the same laboratory under identical conditions. The results using this method were found to correlate well with those of the method of Malloy and Evelyn.[3] Direct acting bilirubin was also determined on random samples by the method of Malloy and Evelyn.

Each infant undergoing phototherapy was placed in the light chamber (within 1 hour of birth) and exposed continuously to a 60-watt blue incandescent lamp (Osram, General Electric Company, United Kingdom) with a spectral emission mainly in the 440- to 520-nanometer (nm) range (figure 1); this particular lamp produces just the right amount of radiant heat to maintain normal body temperature. The illumination on the skin of the infant (average of readings taken at the head, trunk, and lower limbs) was 25-30 foot-candles compared with a nursery illumination of 3.5-4.5 foot-candles. The average energy output on the infant was 12 microwatts per square centimeter (μW/cm^2) in the 425- to 475-nm range, and 17.2 μW-cm^2 in the 400- to 500-nm range, while that of the nursery was 2.6 μW and 4.1

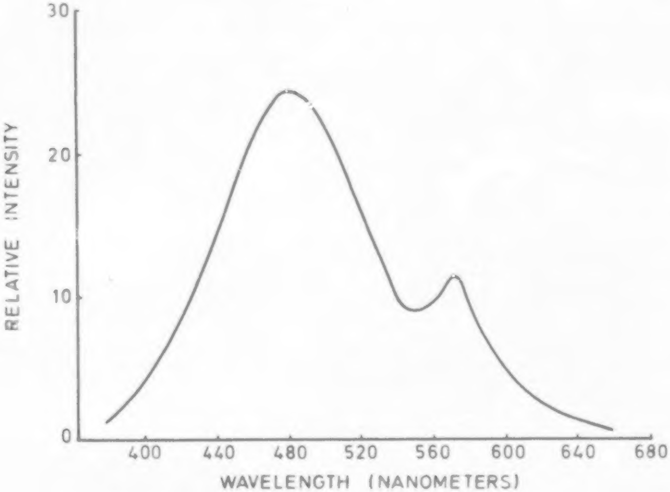

FIGURE 1. Spectral emission of the incandescent blue lamp.

μW, respectively. The measurements were taken by the 11A Photometer/Radiometer (United Detector Technology). The eyes were covered during the duration of phototherapy. The controls were nursed naked in the conventional incubators.

Both groups of infants were nursed in the same manner. Feeds were started at 6 hours of age in the "healthy" infants; the sick infants (table 1) needed intravenous therapy in some cases initially, but were given oral feeds as soon as possible.

The results were subjected to statistical evaluation.

The infants were discharged usually at a weight of 1,900 to 2,000 grams, and a followup study was made on both groups.

RESULTS

Altogether, 128 infants were studied, 68 with phototherapy and 60 without (controls). The two groups were comparable in all respects (see table 1).

The phototherapy group of infants (figure 2) had lower bilirubin levels. This finding became significant on day 4 ($p<0.01$) and day 5 ($0.05>p>0.02$). Seven infants in the control group needed exchange transfusion, while none in the phototherapy group needed it—a difference that was significant ($p<0.02$). Three infants were given an exchange transfusion on day 4, and four on day 5 of life. These infants were excluded from the control group subsequent to the exchange.

The vast majority of infants in both groups reached their peak bilirubin levels in days 4, 5, and 6 of life (figure 3): the average of the peak values were also highest during these days. The difference in the bilirubin levels was significant on day 4 ($0.05>p>0.02$) and day 5 ($p<0.01$). This significant difference occurred even though the seven infants needing exchange had most likely not reached their peak at the time of exchange. Only two infants in the control group reached their peak on day 3 compared with six in the phototherapy group.

TABLE 1. *Comparative data of phototherapy and control infants*

Comparative data	Phototherapy group	Control group
No. of infants	68	60
Weight (grams) [1]	1,660 ± 293	1,645 ± 300
Gestation (weeks) [1]	33.8 ± 2.3	33.6 ± 2.4
Hemoglobin (grams/100 ml) [1]	18.0 ± 3.0	18.2 ± 2.5
No. of sick infants [2]	11	8
Male: female ratio	30:38	28:32

[1] Mean plus or minus standard deviation indicated.

[2] Includes hyaline membrane disease, aspiration pneumonia and severe depression

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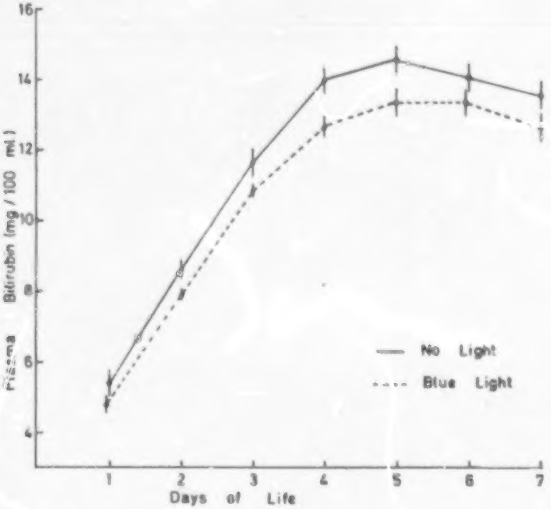

FIGURE 2. Daily mean (with standard error) bilirubin levels of phototherapy and control groups. (Reprinted with permission from Tan, K. L., and Wong, H. B.: *Clinical Pediatrics*, in press.)

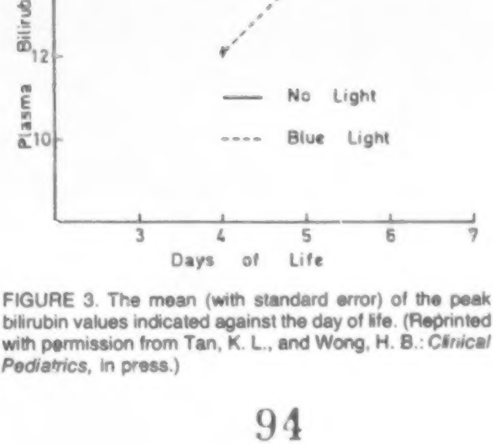

FIGURE 3. The mean (with standard error) of the peak bilirubin values indicated against the day of life. (Reprinted with permission from Tan, K. L., and Wong, H. B.: *Clinical Pediatrics*, in press.)

The average time for the bilirubin level to reach 10 mg/100 ml or lower was hardly different in either group: 10 days in the phototherapy group compared with 11 days in the control group.

The direct acting bilirubin did not exceed 1 mg/100 ml in any of the random samples in which it was determined.

Subsequent followup of the infants demonstrated equal rate of growth physically in weight (figure 4) and head circumference (figure 5) in both groups. The milestones were also very similar. Previous followups of the infants exposed to incandescent lamps for thermotherapy also indicated the harmless nature of this form of exposure to radiant heat, mainly from the yellow incandescent lamps.

DISCUSSION

Hyperbilirubinemia is a frequent complication of prematurity.[2,4] The present study indicates that there is a higher incidence in the Singapore Chinese premature infant compared with the prematures in the West. This result is to be expected as the incidence of severe jaundice even in normal full-term infants in Singapore is also very high.[5] The present study in fact demonstrates an incidence comparable to those studies made in the West before early feeding was instituted.[4,6] In this study, however, feeds were started at 6 hours of age. The use of a simple and effective method to lower

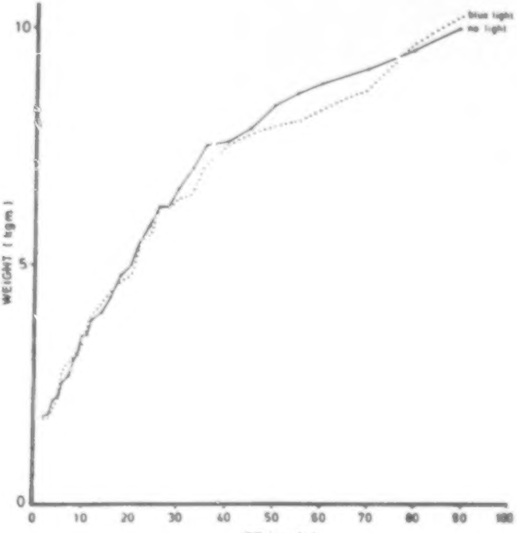

FIGURE 4. Weight growth curves during followup of infants with phototherapy and controls.

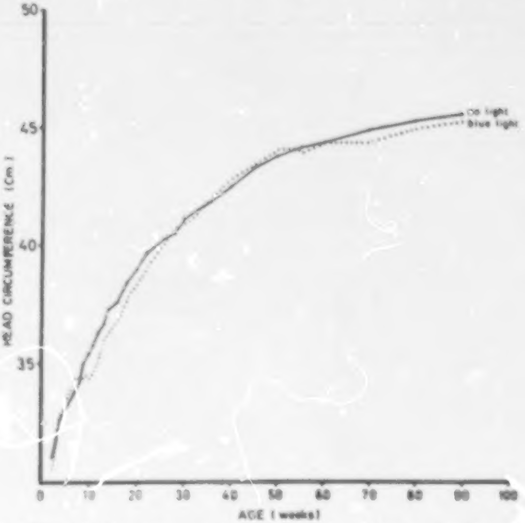

FIGURE 5. Head circumference growth curves in infants with phototherapy and controls.

this high incidence would therefore seem more than justified provided no side effects of a serious nature would result. Phototherapy fulfills this requirement adequately. Apparently, the pigmentation of the skin of the Chinese infants is no barrier to its beneficial effects even with the low level of illumination of the present study.

Incandescent lamps have not been recommended for phototherapy.[7] The present study indicates that such lamps can be effective even though their effectiveness is very much less than that of fluorescent lamps. The intensity of illumination is much lower than that used by other studies so far. Light intensity is an important factor for effective phototherapy, but continuous illumination is just as important a factor if not more so. The lowest practical level of continuous illumination should be recommended.[8] It is quite obvious that the method of illumination used in the present study is far from ideal for maximal effectiveness in phototherapy. It should not be the method of choice in the ideal situation, and in fact is now being gradually replaced by fluorescent lamps by the author in his further studies on this subject. Under other circumstances, especially where radiant heat is also required, it would seem to be a very useful method of providing continuous effective photo- and thermotherapy.

The normal development of the infants in both groups is not unexpected, as previous followups of infants kept warm with radiant heat have indicated its completely harmless nature. The intensity of illumination provided by such lamps can hardly be expected to cause any hazard to the premature infant. In fact, many of the grossly premature infants have been kept warm by radiant heat for durations of over 6 weeks without any untoward effects.

SUMMARY

The radiant heat from incandescent lamps has been used to keep newborn premature babies warm in the Kandang Kerbau Hospital, Singapore, for over 5 years. This form of "thermotherapy" has been found to be not only very convenient and inexpensive, but also very effective, providing instant heat for the infants; no untoward side effects have been encountered.

In the present study, blue incandescent lamps with a spectral emission mainly in the 440 to 520 nanometer range, were used to provide not only thermotherapy, but also phototherapy. Altogether, 128 infants were studied, 68 with and 60 without phototherapy. In spite of the low energy output of the lamps in the range effective for phototherapy, a significant decrease in bilirubin levels was achieved in the phototherapy group.

Followup of the infants indicated no untoward side effects in the phototherapy group; the progress mentally and physically in either group was similar. Incandescent blue lamps are therefore effective for both photo- and thermotherapy, and though not the most effective for phototherapy, they are useful (and safe) in situations that are far from ideal.

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Discussion

Dr. Lucey: I think your study is very interesting. I think that this is the least amount of radiation exposure I have seen with documented proof that it has an effect on serum bilirubin. Would you give us the levels of light intensity in the two groups?

Dr. Tan: The energy output in the 425 to 475 nanometer range was 12 microwatts per square centimeter. In the 400 to 500 nanometer range, it was 17.2 microwatts in the phototherapy group. In this particular study we used blue bulbs to keep the infants warm as well as give them light.

Dr. Brown: What about the controls?

Dr. Tan: They were in the controlled incubators. The energy output of the room's light was only 2.6 microwatts in the 425 to 475 nanometer range and 4.1 microwatts in the 400 to 500 nanometer range.

Dr. Brown: So it was not blue light versus yellow light?

Dr. Tan: No, this was blue light versus blue light.

Dr. Indyk: It is interesting to note that simultaneous thermotherapy and phototherapy were originated by Cremer, Perryman, and Richards (*Lancet*, 1:1094, 1958). In their paper, the height of the lamp from the infant is adjusted to make use of the small amount of heat in keeping the infant's body temperature at 90 to 100 degrees Fahrenheit.

Dr. Tan: In the present study, I am using incandescent bulbs to keep them warm, because I find the fluorescent lamps that I am using are not sufficient to keep infants warm. The babies are completely exposed. We believe that the radiant heat can be extremely effective.

Dr. Indyk: You are not going to get much direct heating from the fluorescent bulbs.

Dr. Lucey: The heating effect of light may be a very important part of the mechanism by which light works.

Dr. Gartner: With regard to the heating or temperature effects on serum bilirubin levels, in the paper that we reported last year on jaundice in the breast-fed baby during the first 4 days of life (B. B. Dahms et al. *J. Pediatr.*, 83:1049, 1973), we observed a group of fully breast-fed infants who had what we might call milk fever. Their rectal temperatures were between 101 and 103 degrees Fahrenheit, and no detectable cause was found after extensive workup. That group of febrile babies had peak serum bilirubin concentrations half that of the other breast-fed afebrile babies. This observation has led me to wonder if body temperature or exogenous heating may have rather potent effects, either on bilirubin transport or metabolism or on the maturation of these processes.

Dr. Brown: Getting away from the subject of temperature and on to the blood, you made two statements that I would like to ask you about. In the group of small-for-gestational-age babies who do not have lower-than-expected bilirubin, were you able to associate that with the degree of polycythemia, which is very common in that group?

Dr. Gartner: I have not yet studied that group in as detailed a manner as it deserves, but will do so in the near future.

Dr. Brown: The other one was the opposite. When you said that the hematocrit was continually declining, I was wondering if you related that all to gestational age differences, because you had both small and small-for-gestational-age babies in your test group and that is the group in which you would expect that pattern?

Dr. Gartner: We have not yet performed that detailed an analysis of the study population. I suspect that the pilot study is too small for statistical significance in subgroups even if there are apparent differences. In the larger study this should be possible.

Dr. Ostrow: Just a brief comment on what we know about fever and liver function. The best study (P.D. Berk, T.S. Blaschke, and J. G. Waggoner. *Gastroenterology*, 63:472–481, 1972) used bromosulphalein kinetics to show that fever did not affect the uptake into the liver cell nor the transfer into the bile, but increased reflux back to the plasma. We do not know if this is applicable to bilirubin.

Dr. Odell: The increased circulation in the periphery (extremities) can amount to about a 10-percent redistribution of the circulation of an infant. That volume is quite significant.

Dr. Brown: Are you raising the probability that you could augment the effect of phototherapy by bringing blood and bilirubin toward the photodynamic action in the periphery?

Dr. McDonagh: It takes time for the skin to refill with bilirubin so you might as well switch the light off until it is refilled. If you increase the refilling by increasing the circulation, then the thermal effect may well enhance the effect of phototherapy.

Dr. Johnson: Just a point with regard to heating. I did not understand Dr. Tan to say that he was overheating his babies. He was only heating them to an optimal level. Dr. Ogawa was using a fan to prevent them from overheating while they were in the incubator. We do not want to either over- or underheat the skin.

Dr. Indyk: If you analyze the data comparing the three different light sources, you will see which is most efficient. It turns out that daylight is the least efficient. Dr. Tan advises us to use much lower light levels. I agree that we are probably wasting most of the photons and should decrease total light dose.

Dr. Lucey: Dr. Gartner, it seems to me that in your study you were doing a large number of exchange transfusions. On 20-odd babies you did a total of eight exchange transfusions. This would mean that you would be doing an average of 40 exchange transfusions per 100 babies. Do you think that this would be desirable? Your criteria for doing an exchange transfusion were very cautious and quite low. I think the complications of exchange can become a significant risk. Some of the complications of exchange transfusions are still unknown.

Dr. Gartner: I do not have figures for our nursery, but I think that we are indeed doing a large number of exchange transfusions. As a result of our very extensive experience, our morbidity attributable to exchange transfusion is extremely low.

Dr. Hodgman: I do not have exact figures, but looking at our study, one of the areas of most concern to me and our unit is this large increase in exchange transfusions in the nonphototherapy-treated infants. My preliminary figures came out to exchanging some 30 to 50 percent of the babies.

Dr. Odell: I have not used any phototherapy, and my exchange rate in the under-2-kilos infant is of the order of 10 percent.

Dr. Lucey: This is something that has always intrigued me. The incidence of jaundice may vary, on an unexplained basis, from one nursery to another.

Dr. Hodgman: The difference between Dr. Odell's babies and my babies is that half of ours are Spanish American, and most of Dr. Odell's patients are black.

There are distinct racial differences in the incidence of jaundice. I am not sure that this is the whole explanation, but it is a large part of it.

Dr. Lucey: What is the composition of the nursery at the Albert Einstein Clinic?

Dr. Gartner: About 40 percent black, 40 percent Puerto Rican, and 20 percent white.

Dr. Odell: Our premature-infant population is about 60 percent black. The large majority of the non-blacks are white, but there is about a 10 percent American Indian.

Dr. Karabus: I am preempting just a little bit of my time on this point of exchange transfusion. We have a different cause altogether. In healthy children, we have done exchange transfusions in 26 percent. These are healthy, and mainly full-term babies, and one-quarter are receiving exchange transfusions.

Dr. Lucey: I wonder if there is any evidence at the moment that light has affected the bilirubin binding capacity in an adverse way?

Dr. Odell: In my experience with the salicylate binding tests of jaundiced sera from infants in the hospitals that are adjacent to us, we have looked at phototherapy- and nonphototherapy-treated babies. We find that the saturation index done by the salicylate method is higher per given level of bilirubin in phototherapy-treated babies. Part of the explanation for this, I think, is because of the temperature problem. We find the fatty acid levels for half of those babies treated by phototherapy to be elevated. That elevation may be due to improper temperature control, which may cause an adverse effect on metabolism. We have no control over that.

Dr. Lucey: Dr. Odell, you had some observations as to the effect of bathing the infants with soap and the effect on the salicylate index.

Dr. Odell: When we were told that we should not use Phisohex, we went to castile soap because it was a mild soap. Another hospital, however, decided to use Ivory soap. We noticed higher serum fatty acids levels in the infants. I asked Proctor and Gamble whether it was possible to directly absorb soap through the skin. They said that they had no data and had not tested for that. We cannot say whether in washing the baby the nursing personnel accidentally got it in the baby's mouth and it was swallowed or whether there was absorption from the skin surface. This happened with six infants in the course of a week. Since the hospital has now stopped using soap, we have not had the opportunity to repeat the observation. The observation remains anecdotal.

Dr. Lucey: It brings up another area of inadvertent treatment of infants. The idea that a simple soap like this can have an effect on something as complicated as a serum salicylate binding test has to be kept in mind.

Dr. Zuelzer: Does anybody know anything about the basic metabolism of albumin when babies are put under the light?

Dr. Brown: We have carefully followed albumin during the course of phototherapy and this does not change. There can be exceptions.

Phototherapy of Neonatal Jaundice at a General Children's Hospital

Cyril D. Karabus

It has been many years since publication of the report of Cremer, Perryman, and Richards[1] on light treatment of neonatal jaundice. Although its exact mode of action is still uncertain, phototherapy has now become an accepted and widely practiced[2] form of treatment for neonatal jaundice. Two main points of controversy regarding its use still exist, however. There are, first, the indications for light treatment, and second, the hazards, if any, of this therapy.

INDICATIONS

The main indication for phototherapy appears to be in hyperbilirubinemia of prematurity.[2-4] In hemolytic disease of the newborn, the effect of light is unpredictable, but several workers have shown a decrease in the number of exchange transfusions required in light-treated infants with ABO,[5,6] Rh,[7] and unspecified hemolytic disease.[4] Phototherapy has also been effective in lowering bilirubin levels of infants with the Crigler-Najjar syndrome.[8-10] This leaves us with the term infant with unexplained hyperbilirubinemia. It has been stated that this condition is so rare and the risk of brain damage is so small that light therapy should be seldom or rarely indicated.[2,4] Our experience, at a nonmaternity children's hospital, is different. These infants form the bulk of our admissions with jaundice, require more exchange transfusions than any other single diagnostic group, and may develop severe brain damage.

What the indications are for the commencement of phototherapy in all these conditions is also not clearly defined. Our policy has been to treat only established hyperbilirubinemia and, in otherwise well infants, to use the bilirubin level as the main guide for starting treatment.

HAZARDS

Of the acute side effects, fever, skin changes, increased stool, and insensible water loss are not uncommon, but are not of major practical concern. More serious, although entirely theoretical at the present time, are the suggested long-term sequelae of light therapy. Fears have been expressed as to the possible toxicity of the photodegradation products of bilirubin and about undesirable or even dangerous direct or indirect effects of light itself on the treated infants.[3]

In this presentation I would like to discuss our indications for the use of phototherapy, the diagnostic makeup and management of the patients, and observations concerning possible acute and long-term side effects of light treatment.

The Red Cross War Memorial Children's Hospital is the only children's hospital in Cape Town (the city and its surrounding area has a population of about 1 million). A neonatal jaundice unit was established in December 1969 in order to collect the many jaundiced infants referred to the Children's Hospital, offer a proper diagnostic workup, and standardize their treatment. Previously, jaundiced neonates had been scattered throughout the medical wards of the hospital, investigated inadequately, treated variably, and not followed up.

PATIENTS AND METHODS

In the 4 years from January 1970 to December 1973, 1,765 infants were admitted to the jaundice unit (figure 1). This represents just over 2 percent of births in the Cape Town municipal area (22,000 per year). As no

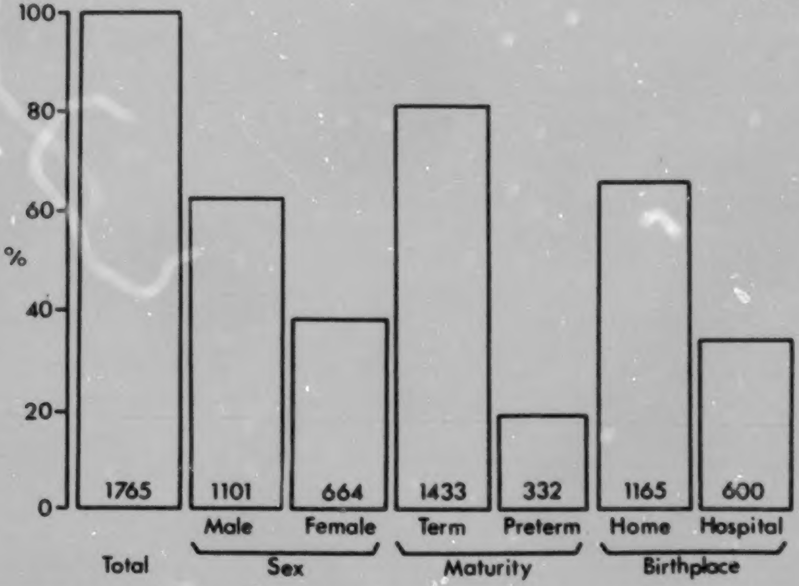

FIGURE 1. Admissions to jaundice unit of the Red Cross War Memorial Children's Hospital, Cape Town, 1970–73.

deliveries are done at the Red Cross Hospital, all patients were admitted from outside the hospital. There was a marked male predominance—62 percent; the great majority were full term—81 percent—as against 19 percent preterm or low-birth-weight infants; 66 percent of the patients were born at home, with the remainder born in hospitals. Most of these latter infants had been discharged home early from local maternity units. A few were referred from country hospitals around Cape Town with an occasional patient from as far as 600 miles away. The majority of the neonates were referred by the midwife who did the home delivery or the maternity hospital midwife doing her home followup visit, but some were referred by the family, local clinic, or country hospital practitioner. A capillary blood bilirubin service was available to midwives in the municipal area, and they had instructions to refer to the hospital all babies with a serum bilirubin level of 12 milligrams percent (mg%) or more.

The criterion for admission and initiation of phototherapy in well babies was arbitrarily and tentatively set at an unconjugated serum bilirubin level of 4 mg% below Diamond's exchange transfusion curves [11] for term (figure 2) and preterm infants (figure 3). A small modification was made to Diamond's curve for preterm infants in that the exchange transfusion line was flattened out at 18 mg% instead of 20 mg% by 96 hours of age. As most patients were a few days old when admitted, the indication for light treat-

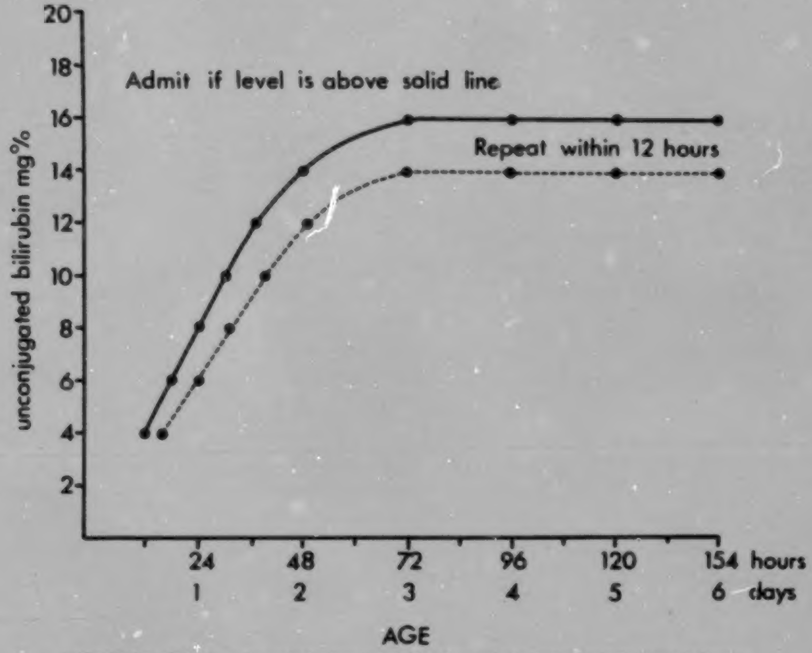

FIGURE 2. Criterion for admission and initiation of phototherapy in term infants.

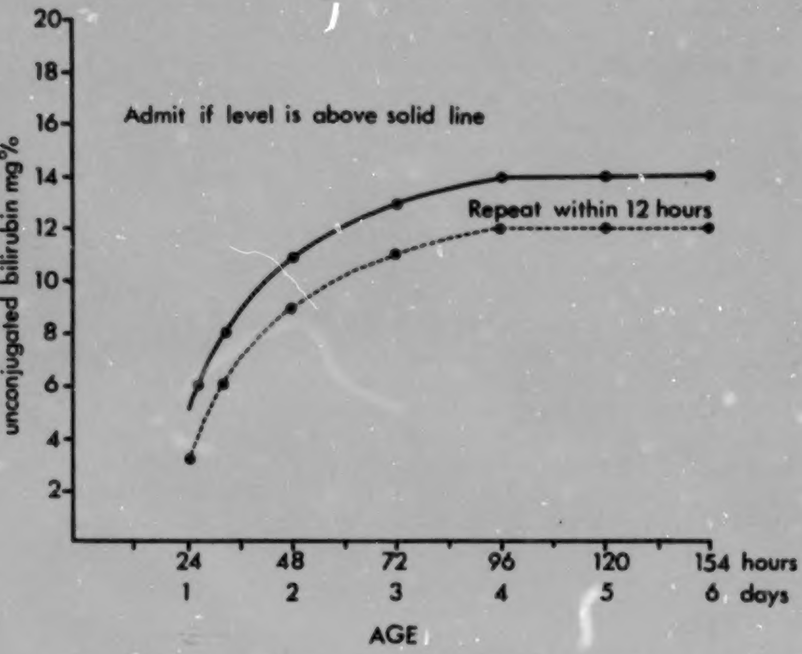

FIGURE 3. Criterion for admission and initiation of phototherapy in preterm infants.

ment was thus generally a serum bilirubin level of 16 mg% in term and 14 mg% in preterm infants. Babies whose bilirubin level did not qualify them for admission were seen again by the outpatient resident at 12- to 24-hour intervals for repeat bilirubin estimations. Very immature or ill infants were rarely seen—they were admitted immediately and other criteria in addition to the bilirubin level were taken into account when deciding on treatment.

Light treatment was given in a specially constructed unit 1.8 by 0.6 meters in size, with space for four infants in bassinets. In addition, another unit fitting over a single bassinet or incubator was used occasionally. The large unit contained 23 daylight fluorescent lamps placed 25 centimeters above the patients, with a sheet of Plexiglas interposed between lamps and patients. The small unit contained 10 daylight lamps. The illuminance at the upper body surface of the patient was 400 foot-candles, and the irradiance between 400 and 500 nanometers was 0.9 milliwatts per square centimeter.

The infants were completely naked except for pads covering their eyes and were continuously exposed to light therapy until the bilirubin level had fallen below 13 to 15 mg% in the well preterm and term babies and to lower figures in the ill infants. The duration of treatment varied from less than 24 hours to 5 days. Serum bilirubin concentrations were done once or twice daily (or more frequently if indicated) on heelprick blood samples in an AO Bilirubinometer or on venous samples by the method of Evelyn and Malloy.[12] The two methods showed good correlation. The infants were weighed daily, and their temperatures were checked hourly while receiving phototherapy.

Exchange transfusions were performed when the unconjugated bilirubin level reached 18 mg% in the preterm and 20 mg% in the term infants. In the few very immature or ill babies, transfusions were done earlier than this. After completion of the procedure, phototherapy was continued.

The cause of the hyperbilirubinemia was carefully studied. A special record card was devised in which an appropriate history, examination, and investigation were entered. Maternal blood was taken for Wasserman reaction and grouping, and antibodies were looked for using an Ortho Selectogen cell panel, as well as the 2-mercaptoethanol test for immune anti-A and anti-B antibodies where an ABO incompatible situation was present. Blood grouping, Coombs test, blood count and film, reticulocyte count, and Motulsky test for glucose 6-phosphate dehydrogenase (G-6-PD) deficiency were done on the infant's blood. For the past year we have also measured red cell acethylcholinesterase activity in an attempt to improve identification of ABO hemolytic disease. Urine was examined for infection and reducing sugars, and other investigations were performed when indicated.

Patients were seen at the neonatal jaundice outpatient clinic at the age of 3 months or earlier if indicated. A full general examination with assessment of growth and development and a blood count were done together with an audiogram in those infants with initial bilirubin levels close to or above exchange transfusion levels. In these latter infants or in others where an abnormality was detected, a further assessment at 1 and sometimes at 2 years of age was done.

RESULTS

Diagnosis

The main diagnostic categories of the infants admitted are shown in figure 4. The largest group (59 percent) was made up of 1,043 full-term infants with unexplained hyperbilirubinemia. Infants with hyperbilirubinemia of prematurity totaled 275, or 16 percent. Confirmed or suspected ABO hemolytic disease was seen in 338 (19 percent) of the patients and deficiency of G-6-PD in 48 (2.7 percent). The other diagnoses are listed in decreasing order of frequency and occurred in less than 2 percent of the infants. Enclosed hemorrhage, mainly cephalhematomas, Rh hemolytic disease, and infections were most frequent in this group.

Exchange Transfusion

Frequency

The frequency of exchange transfusion in each diagnostic category is

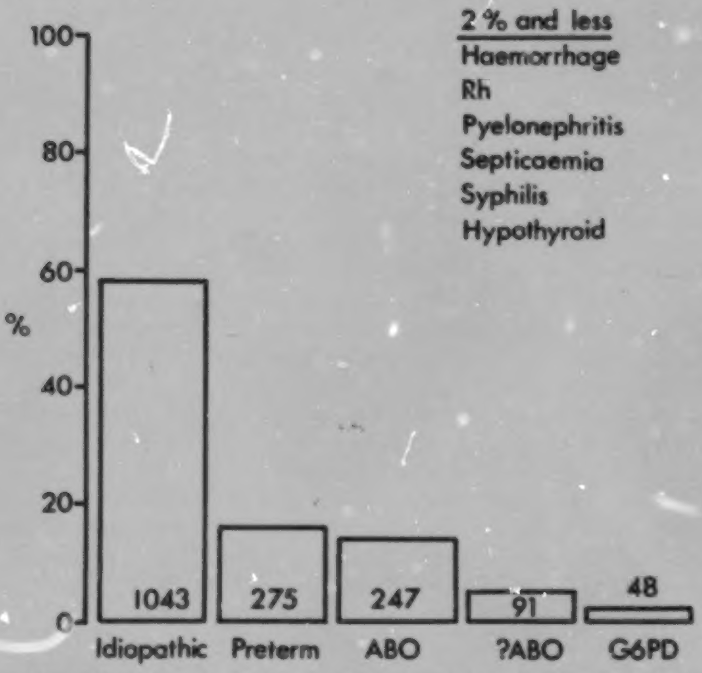

FIGURE 4. Main diagnostic categories of infants admitted to jaundice clinic, 1970–73.

shown in figure 5. Overall 26 percent (460) of the 1,765 infants received one or more exchange transfusions. The incidence was highest in hemolytic conditions—63 percent for Rh, 52 percent for ABO and suspected ABO hemolytic disease, and 35 and 60 percent for cephalhematoma and other enclosed hemorrhage. Only 27 percent of premature and 17 percent of term infants with unexplained hyperbilirubinemia required the procedure.

Number

When one looks at the actual number of patients receiving exchange transfusions (figure 6), it is seen that 246, or 53 percent, of the total were term or preterm infants with neither hemolytic disease nor infection. The procedure was performed on 172 term infants (37 percent) with idiopathic hyperbilirubinemia. This was the largest single diagnostic category, exceeding the 133 infants exchanged with proven ABO hemolytic disease and equaling the 175 with both proven and suspected ABO disease.

Repeat Procedures

Of the 460 infants, 354 received one, 95 two, and 11 had three exchange transfusions (figure 7), making a total of 577 procedures.

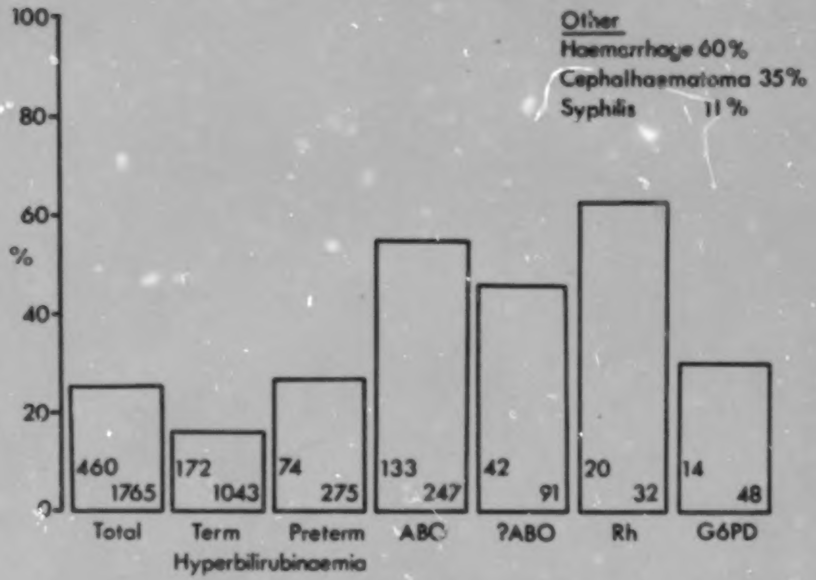

FIGURE 5. Exchange transfusion frequency, 1970–73.

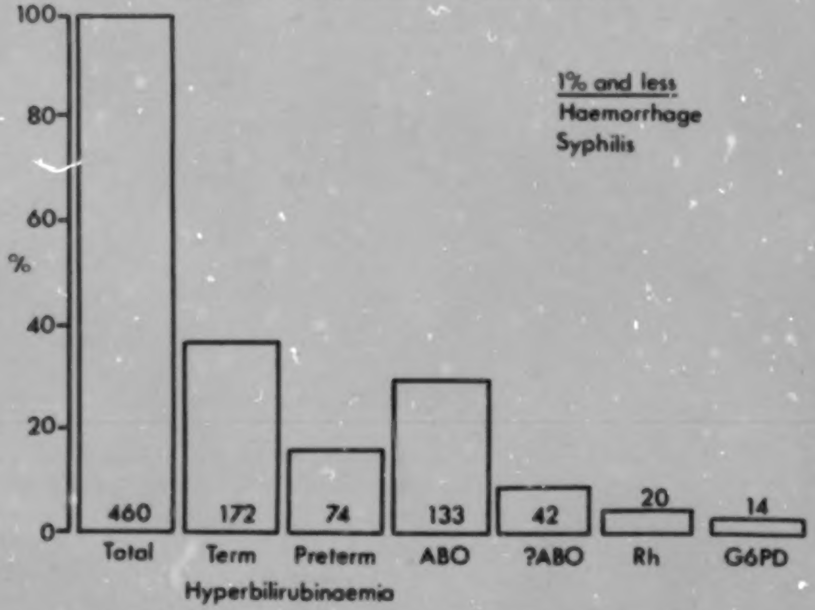

FIGURE 6. Number of infants receiving exchange transfusion, 1970–73.

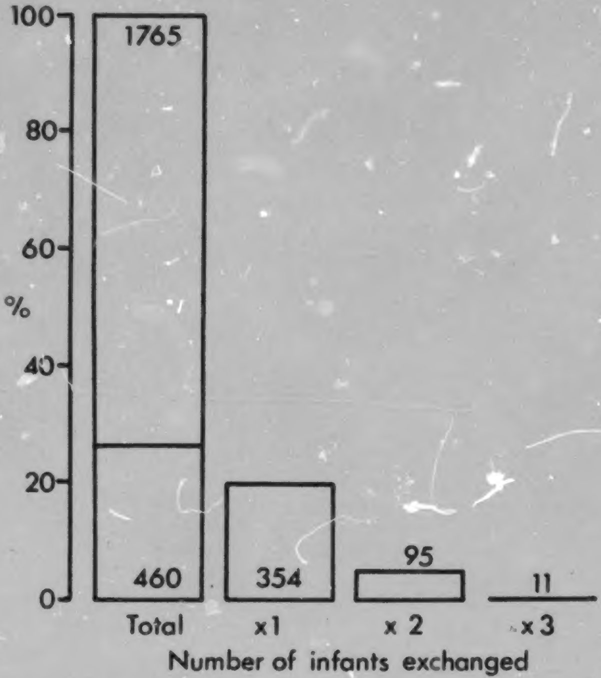

FIGURE 7. Total number of exchange transfusions, 1970–73.

Mortality and Complications

One infant died less than 6 hours after, one 12 hours after, and two patients died more than 24 hours after exchange transfusion. In the latter three, early pneumonia, necrotizing enterocolitis with perforation and a subdural hematoma were found at autopsy. If all four deaths are regarded as being related to the procedure, the mortality rate is 0.9 percent.

One of the infants exchanged is known to have developed a portal vein thrombosis.

Phototherapy

Failures

Analysis of bilirubin levels shows that in 449 (98 percent) of the 460 patients receiving an exchange transfusion, the procedure was indicated at the time of admission. In only 11 of the infants was there time for a trial of phototherapy before transfusion became necessary, and these might be classed as phototherapy failures. Eight of them had hemolytic disease and three had hyperbilirubinemia of prematurity. There were no special features in these latter three patients to account for the lack of response to phototherapy but all, and indeed the whole group of 11, were close to exchangeable bilirubin levels when light treatment was commenced.

Repeat exchanges were necessary in 106 infants. Two procedures were done in 95 patients (table 1). Sixty-seven had isoimmune hemolysis, G-6-PD deficiency, or enclosed hemorrhage, and their mean unconjugated bilirubin levels ranged from 23 mg% to 29 mg%. Twenty-eight patients (22 term and 6 prematures) had hyperbilirubinemia with mean unconjugated bilirubin levels of 27 mg% and 30 mg%, respectively. Three exchange transfusions were done in 11 patients (table 2), all but one having severe ABO or Rh hemolytic disease. The exception was a premature infant with hyperbilirubinemia of 37 mg%.

Effect

Figures are not available for the number of exchange transfusions done at Red Cross Hospital prior to the introduction of phototherapy.

The severity of jaundice in the 1,765 patients is shown in figure 8. Of the total, 33 percent of the patients had unconjugated serum bilirubin levels of 20 mg% or above. Levels between 15 and 20 mg% were seen in 1,077 or 61 percent of the infants. Of these, as has been mentioned previously, only 11 patients given a trial of phototherapy were shown to have the bilirubin rise to exchangeable levels.

TABLE 1. *Bilirubin levels in infants receiving two exchange transfusions* [1]

Condition	No.	Unconjugated bilirubin (mg%)	
		Range	Mean
ABO	56	18–39	28
Rh	4	19–35	25
G-6-PD ↓	4	21–35	29
Hematoma	3	20–32	23
Term	22	21–38	27
Preterm	6	23–37	30

[1] *N*=95 infants.

TABLE 2. *Bilirubin levels in infants receiving three exchange transfusions* [1]

Condition	No.	Unconjugated bilirubin (mg%)	
		Range	Mean
ABO	8	27–36	31
Rh	2	32–39	36
Preterm	1	37	37

[1] *N*=11 infants.

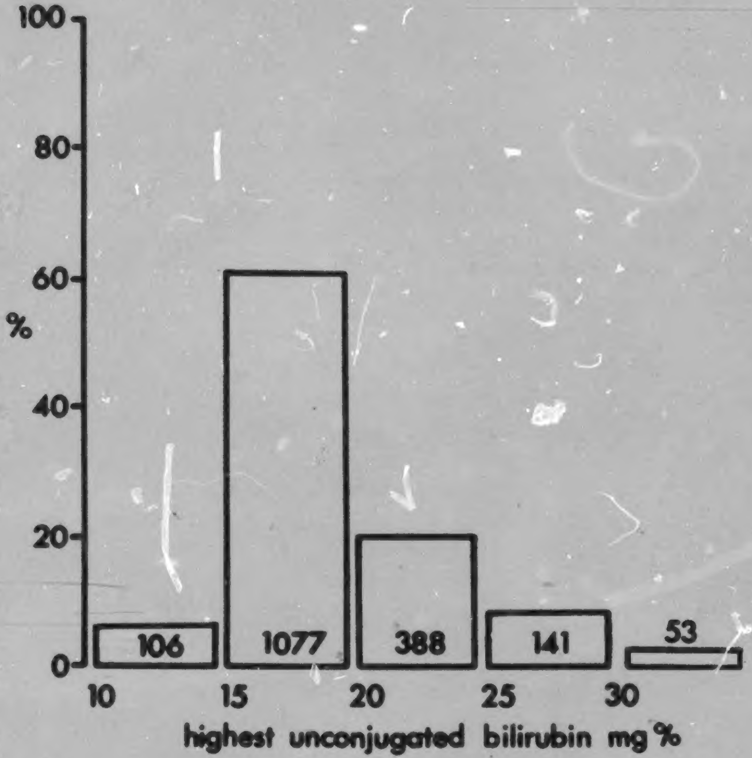

FIGURE 8. Severity of jaundice of 1,765 patients.

Jaundice in term infants with hyperbilirubinemia

Similar analysis of the severity of jaundice in 1,043 term infants is shown in figure 9. Here only 22 percent of the patients (as compared to 33 percent of the infants overall) had unconjugated bilirubin levels of 20 mg% or greater. However 70 percent of the babies had levels between 15 and 20 mg%. In none of these 727 patients did the bilirubin level rise above 20 mg% after commencement of phototherapy.

Possible side effects

Ward observations: Green discoloration of the stools, fever, and occasional skin rashes were the only untoward effects noted. No baby became dehydrated as a result of phototherapy. No cases of bronze baby syndrome were seen, although two of the infants were subsequently found to have hepatitis and biliary atresia, respectively.

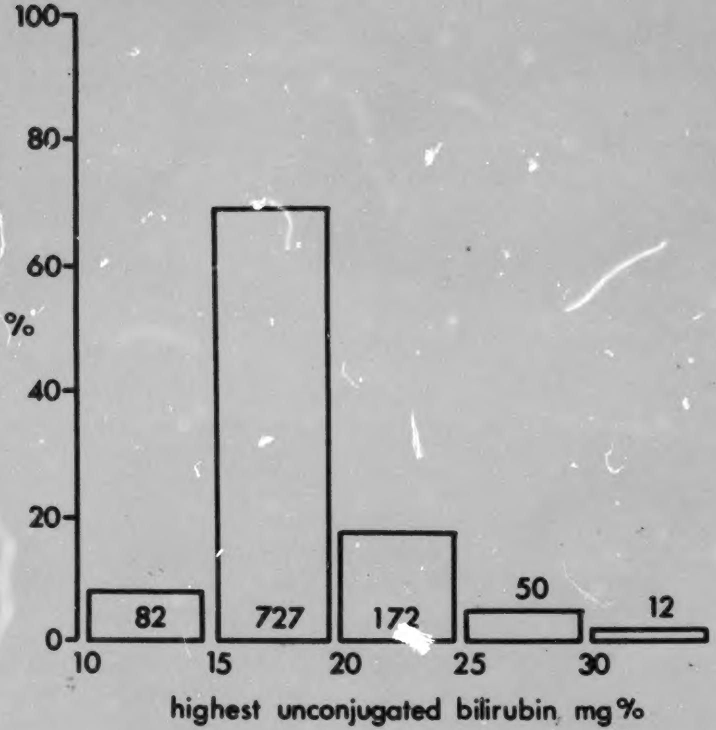

FIGURE 9. Severity of jaundice in 1,043 term infants.

Outpatient observations: The possible complications of phototherapy follow:

1. *Growth:* Figures on the weights of 338 of the infants at 1 year of age and of 97 at 2 years of age are shown in table 3. Eighteen percent of the 92 low-birth-weight and preterm infants and 6 percent of the 246 term infants were below the Boston third percentile for weight at 1 year of age. By the age of 2 years, 15 percent of the low-birth-weight and 4 percent of the term infants were below the third percentile. Sixteen percent of the low-birth-weight and 10 percent of the term infants (273 in all) at 1 year of age were below the third percentile for head circumference (see table 4). At 2 years, of a total of 95 infants, 14 percent of the low-birth-weight and 8 percent of the term infants, were below this level.

In a survey in Cape Town of 1,000 apparently healthy 1-year-old children of approximately similar socioeconomic background to the phototherapy group, 26 percent were found to be below the Boston third percentile for weight.[13] No comparable local figures for head circumference are available, but Ounsted and Taylor [13] found that 16 percent of a group of small-for-dates infants in England were below normal at 1 year of age.

TABLE 3. *Weights of infants after phototherapy*

Infant group	1 year		2 years	
	No.	<3°	No.	<3°
Preterm	92	18%	27	15%
Term	246	6%	70	4%
Control	1,000	26%	—	—

Note.—<3° indicates less than 3d percentile.

TABLE 4. *Head circumference by percentile of infants after phototherapy*

Infant group	1 year		2 years	
	No.	<3°	No.	<3°
Preterm	77	16%	27	14%
Term	196	10%	68	8%

Note.—<3° indicates less than 3d percentile.

2. *Abnormalities:*

a. *Obvious kernicterus:* Eight infants showed marked indications of kernicterus. Of these, two ill, immature babies with unconjugated bilirubin levels of 25.6 mg% and 36 mg% died shortly afer admission and were shown to have kernicterus at autopsy. Of the six living infants, two were premature infants with severe hyperbilirubinemia (unconjugated bilirubins of 32 mg% and 34 mg%), one was a term infant with Rh hemolytic disease (37 mg%), one had ABO hemolytic disease (39 mg%), and two were term infants without evidence of hemolysis. The first infant weighed 2.73 kilograms at birth, developed jaundice at about 48 hours of age; on admission, aged 80 hours, he had an unconjugated bilirubin level of 34.9 mg%. No blood group incompatibility was present, and the infant showed no anemia, reticulocytosis, or morphologic abnormalities of the erythrocytes. Deficiency of G-6-PD was subsequently demonstrated. The other infant weighed 3.55 kilograms at birth, and on admission, aged 67 hours, he had an unconjugated bilirubin level of 38 mg%. There was no evidence of hemolytic disease. Signs suggestive of kernicterus were present on admission, but he was not acidotic and showed no overt signs of infection. A urinary infection, with isolation of *E. coli*, was the only other abnormality found. Intravenous pyelography did not demonstrate urinary tract pathology.

b. *Other:* Two infants were found to be microcephalic—both had a normal head circumference at birth. At 2 years of age their head circumferences were 43 and 44.5 centimeters, respectively. Their highest unconjugated bilirubin levels were 18.4 and 15 mg%, and neither child had had any neurological illness during infancy, which might have accounted for their microcephaly.

> One child appeared to have a constitutionally large head (circumference 47 centimeters) but was otherwise completely normal at 1 year of age. Another child had cerebral gigantism. He weighed 4.73 kilograms at birth and his bilirubin level reached 15.4 mg%. At 2 years and 3 months, he weighed 36 kilograms, had a head circumference of 55 centimeters, and was markedly retarded. Hearing loss was initially found in 11 of 389 infants tested, but in seven of these, repeat audiometry has shown normal hearing.

None of the other infants followed for 2 years, and longer in a few instances, showed any obvious abnormalities of growth or development.

DISCUSSION

Before discussing our results, I feel one should emphasize that the group of infants we have seen is very different to those previously published or discussed today. These are neonates with established jaundice, often very severe jaundice. They are referred to our hospital from a widespread area and by many different people, although the majority of these (i.e., the midwives) belong to a single municipal organization. Apart from their jaundice, the patients are, on the whole, healthy infants. Although in 19 percent the birth weight was below 2.5 kilograms, very immature infants were extremely rare. The majority of patients (two out of three) were born at home. This is therefore a group of infants not very comparable to the 'pampered' hospital-born infant carefully watched from birth under ideal conditions in a newborn nursery by a small group of skilled attendants with all treatment facilities immediately at hand.

Indications

As mentioned, our patients were given light therapy only when jaundice was (1) established and (2) established to the fairly significant degree of only 4 mg% below the bilirubin level that was formerly generally accepted as an indication for exchange transfusion. In practice, as most of the infants were 2 or 3 days old at the time of admission, this meant an unconjugated bilirubin level of 16 mg% and above for term and 14 mg% or more for preterm infants. The cause of the jaundice was not taken into account when phototherapy (or for that matter, exchange transfusion) was being considered. As a result of this admission policy, 59 percent, by far the largest number of patients given phototherapy, were healthy term infants with unexplained hyperbilirubinemia.

Are our indications for phototherapy correct? This is really a double question: Should all these term hyperbilirubinemics be treated? If so, what should be the indication for commencing phototherapy not only in these infants but also in the other diagnostic categories in which the use of phototherapy is less controversial?

In considering whether phototherapy be used for term infants with unexplained hyperbilirubinemia, I feel the decision is simple. Given the fact that 22 percent of these infants had an unconjugated serum bilirubin level of 20 mg% or greater, it follows that either one does not consider exchange transfusion necessary for them or that some measures to prevent transfusion (i. e., phototherapy) should be instituted. For those prepared to allow bilirubin levels to rise to higher levels in these infants before treatment, it can be pointed out that in 6 percent (62 infants) the unconjugated bilirubin was 25 mg% or more (50 infants between 25–30 mg% and 12 above 30 mg%). Taking 20 mg% as the indication for exchange transfusion, more of these infants required the procedure than neonates with established ABO hemolytic disease. I feel this is good support for the need to use phototherapy in term hyperbilirubinemics. In addition, judging by grossly obvious signs only, there were two term infants without immune hemolytic disease who had bilirubin-induced brain damage. Admittedly, both had other pathology—G-6-PD deficiency and possible urinary tract infection—and they have not been included in the idiopathic hyperbilirubinemic group. There is the suspicion, however, that two out of our eight infants with severe obvious brain damage (and these of course are only the tip of the yellow iceberg of possible brain damage) occurred in term infants with no signs of hemolysis.

Regarding the indications for commencing phototherapy, we found no reason to change our criteria during the years. Although at first glance the fact that we had to do exchange transfusions on 460 infants might seem that the indication for phototherapy was set at too high a level of bilirubin, analysis shows that this is largely due to failure to attend the hospital early enough—that is, late referral rather than hospital delay of treatment.

The effort at present is directed toward getting midwives to refer babies earlier. Until then we propose to retain our present indications for commencement of phototherapy. These, of course, do not necessarily apply to hospital-born infants.

Efficacy

Numerous well-controlled studies have demonstrated the effectiveness of phototherapy.[15–21] Light treatment can be judged on its effect in lowering bilirubin levels and reducing the number of exchange transfusions. Unfortunately, figures are not available for the number of jaundiced infants seen at our hospital let alone the transfusions performed prior to the establishment of the neonatal jaundice unit. In the present group of infants, however, 449 required an exchange transfusion at the time of admission; in only 11 of the remaining 1,316 patients, all of whom had established jaundice of some magnitude, an exchange transfusion became necessary after light treatment was commenced. Of these 11, 8 were ABO hemolytics who were 1–2 mg below the bilirubin level for exchange transfusion on admission; in these instances, the failure of phototherapy to prevent the transfusion was not very surprising, and 3 had hyperbilirubinemia of prematurity. Here it is possible that an exchange transfusion might have been avoided had light treatment been started earlier.

Looking at the prevention of repeat exchanges, once again it is not surprising that some repeats were necessary, despite phototherapy. With pretreatment unconjugated bilirubin levels as high as 39 mg%, light treatment can hardly be blamed for failing to prevent the need for second or third transfusions, especially as most of these patients had hemolytic disease.

The severity of the jaundice occurring in some of the full-term infants with hyperbilirubinemia is underlined by the fact that they made up 22 of the 106 infants requiring more than one exchange transfusion. This group had a *mean* unconjugated serum bilirubin level of 27 mg%.

Untoward Effects

For so simple and atraumatic a treatment, a remarkably long list of side effects had come to be associated with phototherapy.[21] The untoward effects may broadly be grouped into acute (fever, skin changes, and increased water loss) and long-term (affecting growth and neuroendocrine function). On closer examination these two groups might equally well be called observed and theoretical, respectively. As some of the suggested[23] side effects, such as growth retardation, are disproved,[4,24] others, such as the mutagenic or carcinogenic effect of light take their place.[2] It is clear that the acute side effects of phototherapy have not constituted a hazard in our experience or in that of others and should not be a problem in any reasonably well-run nursery. With long-term effects such as carcinogenesis and mutations now being raised, the question of the safety of light will take half a century to answer to everyone's satisfaction. The use of phototherapy becomes largely dependent on the risk of other treatment. Ethically I believe that as no ill effects of light therapy have actually been demonstrated in humans, we are perfectly justified in using this treatment particularly in areas, such as ours, where a small medical staff has a heavy clinical load to cope with. The justification is strengthened by the fact that the only other presently available treatment for neonatal jaundice, exchange transfusion, may be both harmful and, in almost 1 percent of infants, lethal.

I have nothing further to add to what has been said already in regard to the safety of phototherapy except that we have found no ill effects of phototherapy either acutely or, thus far, in the longer term regarding growth or development in our treated infants.

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"Co-Twin Control" Study of the Long-Term Effects of Phototherapy

F. K. Friederiszick

Before going into the subject of the long-term effects of phototherapy, I should like to answer a few general questions that have been raised. Dortmund is an industrial town of 650,000 inhabitants. The annual birth rate has been definitely on the downgrade during the past 10 years. It dropped from almost 10,000 in 1967 to about 5,500 in 1973 (table 1). In principle, this trend corresponds to the birth rate figures in the entire Federal Republic of Germany. The birth rate dropped from 18.2 viable births per 1,000 inhabitants in 1964 to 10.2 viable births per 1,000 inhabitants in 1973 (see table 2).

TABLE 1. *Annual birth rate in Dortmund, 1964–73*

Year	Birth rate
1964	10,716
1965	10,753
1966	10,594
1967	9,957
1968	9,548
1969	8,836
1970	7,573
1971	7,097
1972	6,211
1973	5,544

TABLE 2. *Decline in birth rate in Germany (BRD), 1964–73*

Year	Births per 1,000 inhabitants
1964	18.2
1965	17.7
1966	17.6
1967	17.0
1968	16.1
1969	14.8
1970	13.4
1971	12.7
1972	11.4
1973	10.2

Our gynecological hospital has an annual delivery rate of about 2,000 births. We receive the newborn, however, from a total of 15 obstetric departments that are spread throughout the city and that differ greatly in size. We run a central transport service to bring all premature infants straight to us from the delivery room so that we can take care of them. We also take on all newborns requiring pediatric treatment.

As shown in table 3, the total number of patients treated annually in our children's hospital is about 2,600. Approximately 750 of these are newborn.[2] About half of these are mature births; the other half are premature infants. There are certain variations in some of the years. Premature and mature infants are housed in two different stations.

Phototherapy is performed by us with equipment supplied by Air Shields and by Hanauer Quarzlampen Ltd. At present we have 10 of these units. We use light sources resembling daylight;[1,2] we did not find blue-light lamps more successful in clinical use.

During phototherapy, the newborn infants are always in the incubator. As a matter of principle, we do not apply phototherapy to newborn infants in bed. Radiation is continuous. It is not interrupted even during visiting time. The position of the children is not changed. Their eyes are covered with impervious eye bandages. Radiation is started as early as possible. Duration of therapy depends on the clinical course.[3-5]

Checks on bilirubin levels are carried out several times a day according to the method of Jendrassik and Gróf.[6] Recently, we have been using the "OHC" photo-ictometer, Model II. This instrument enables determination of bilirubin from capillary blood in 5 minutes.

Since 1969 we have applied phototherapy to more than 1,200 infants in our clinic. The number of treated cases has been increasing each year. The most frequent indications for phototherapy were the following:[3,4,7-13]

1. Prevention of hyperbilirubinemia in prematures
2. Therapy of hyperbilirubinemia in all newborns
3. Therapy of Rh and ABO erythroblastosis with or without exchange transfusion

TABLE 3. *Number of admissions, Children's Hospital, Dortmund, 1969–73*

Year	Hospital total	Newborn infants		
		Premature	Full-term	Total
1969	2,692	410	346	756
1970	2,580	396	317	713
1971	2,760	410	378	788
1972	2,636	367	388	755
1973	2,494	351	325	676
Mean	2,632	387	351	736

An occasional interruption of phototherapy became necessary in the beginning only because we did not have enough phototherapy units at our disposal.

In idiopathic hyperbilirubinemia in premature infants, exchange transfusions could be completely omitted because of the introduction of phototherapy. Contrary to other reports,[14] the number of our cases of idiopathic hyperbilirubinemia in full-term infants requiring treatment was almost equal to that in prematures. We believe that the reason for the high incidence of full-term idiopathic hyperbilirubinemia is late or inadequate fluid intake when the newborn does not drink spontaneously after prolonged labor, complicated presentation, or any other birth stress.

In our hospital, exchange transfusions in ABO erythroblastosis are now rare events. The number of exchange transfusions for Rh erythroblastosis has also been significantly reduced. In this case, however, the increasing use of anti-D prophylaxis also exercised some influence. Pronounced anemia made it necessary to effect substitution of erythrocytes through transfusion in almost all hemolytic disease of the newborn after completion of light therapy.[15]

In 1969, Heller, Ballowitz, and Natzschka [16] reported their radiation experiments with blue light in young Gunn rats. They observed disturbed progress, retarded growth, and increased mortality in the newborn animals treated in this manner. Hence they suggested comparative investigations in infants subjected to phototherapy.[17]

These reports prompted us to conduct a "co-twin control" study in prematurely born monozygotic twins. Due to the large number of premature births in our hospital, we were able to conduct this comparative study in 23 pairs of twins in less than 1 year.

The lighter weight infant of each pair of twins was subjected to continual phototherapy for 6 days (144 hours) from the day of birth. The heavier infant did not get phototherapy. In all other respects, therapeutic measures and care were the same in both twins.

The serum bilirubin data obtained by us were similar to those reported by others who had conducted comparative phototherapeutic investigations in underweight newborns.[18–20] Due to the early onset of phototherapy (on the first day of life), the serum bilirubin values remained extremely low and attained an average maximum value of only 4.1 milligrams percent (mg%) on the fourth day (figure 1). The serum bilirubin values in the untreated controls were about twice as high. The difference in serum bilirubin values was significant. In addition, none of the untreated controls attained a critical bilirubin value in the serum (the highest individual value was 12.3 mg%). None of the children required an exchange transfusion.[4,13]

We were particularly careful in comparing the body weights of our twins, bearing in mind the animal experiments I have just mentioned. Fortunately, unsatisfactory weight increase was never observed in the light-exposed twin. When we evaluated all 23 pairs of twins, we set the body

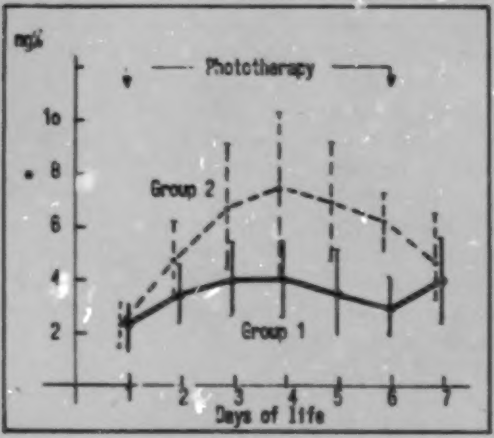

FIGURE 1. Mean daily serum bilirubin levels in 23 twin sets treated with (group 1) or without (group 2) phototherapy. Asterisk (*) indicates mean serum bilirubin level. (Reprinted with permission from *Strahlentherapie* [1] and *Zeitschrift für physikalische Medizin*.[9])

weight at birth to be equal to 100 and compared the average relative weight increase in both cases. It was found that the average initial weight loss in the 23 light-exposed children was lower than in the controls (figure 2). They attained their initial weight level, that is, their weight at birth, earlier, and the relative weight advantage was also maintained during the following weeks.[4,13]

We also found that dehydration or diarrhea had never occurred during phototherapy. The number of stools in the treated group was only 11 percent higher than in the control group, which means the increase was only slight, without any indication of diarrhea.[21]

Renal elimination of the bilirubin derivatives during the days following birth was suggested by the observation that the urine, when taken from both twins at the same time, of the exposed twin always had a darker color than that of the control.

In 1974, we were able to reexamine 19 pairs of twins out of the original total of 23. Of the remaining pairs, two had moved and their address was not known. One pair did not appear for examination, while another pair had died in an accident. Three further pairs of twins were found to be discordant after polysymptomatic similarity diagnosis and blood group examination, so that 16 monozygotic pairs of twins (10 female, 6 male)

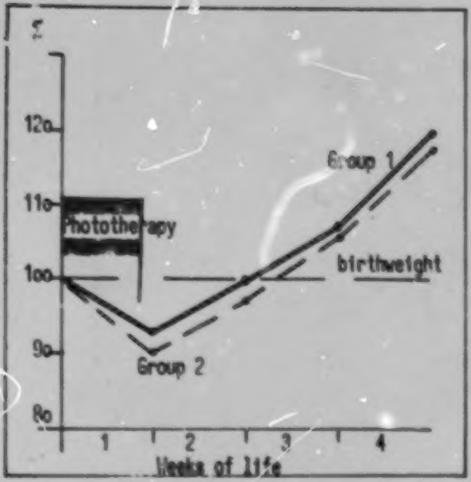

FIGURE 2. Mean relative weight increase in 23 twin sets treated with (group 1) or without (group 2) phototherapy. (Reprinted with permission from *Strahlentherapie*[1] and *Zeitschrift für physikalische Medizin*.[8])

could be evaluated for our study. (Due to the elimination of the discordant pairs of twins, the average values of our preliminary report have changed.)

For purposes of comparison, we extended our studies to 12 monozygotic pairs of twins (6 male, 6 female) where both children had not been exposed. Furthermore, seven pairs of twins (five male, two female) were investigated in the same manner, both children having been subjected to phototherapy. This means that a total of 35 monozygotic prematurely born pairs of twins (17 male, 18 female) were included in the reexaminations (table 4).

The investigations were carried out in cooperation with the Research Institute for Infant Nutrition in Dortmund. Blood groups were determined in our blood bank.

TABLE 4. *Followup study of 35 identical twin sets, 1974*

Treatment	Pairs
Alternately one twin with light, the other without	16
Both twins without light	12
Both twins with light	7

The following investigations were made of each child:

1. History
2. Physical examination
3. Somatometry, according to Tanner [22]
4. Photographs
5. Hemogram
6. Determination of blood groups
7. Development test according to Bühler-Hetzer [23]

The investigators were always the same persons. To avoid any possible bias, they did not know which of the two twins had been exposed to light and which of them had remained untreated. All of the results were recorded on questionnaires or punched cards, so that many parameters not mentioned here can be evaluated later in future scientific research.

RESULTS

The average weight difference at birth between the exposed and the untreated group was 179.38 grams (table 5). In the reexamination at the age of 4 years, the average weight difference between the treated and the untreated group was 175 grams. On the average, the exposed children who had been of lighter weight at birth remained lighter even 4 years later; usually, this also applies to individual cases. The weight difference was very small, however.

The average difference in length at birth between the radiated and untreated twins was 0.06 centimeter (table 6). On reexamination at the age

TABLE 5. *Mean weight in 16 identical twin sets with or without phototherapy*

Therapy	Birthweight [1] (1969)	Weight 4 years later [2] (1974)
Light	2,068.75	15.68
Control	2,248.13	15.85
Difference	[3] 179.38	[4] 0.175

[1] In grams.
[2] In kilograms.
[3] 8 percent.
[4] 1 percent.

TABLE 6. *Mean height in 16 identical twin sets with or without phototherapy*

Therapy	Length at birth (centimeters)	Length 4 years later (centimeters)
Light	46.63	101.1
Control	46.69	101.3
Difference	[1] 0.06	[2] 0.2

[1] 0.13 percent.
[2] 0.19 percent.

of 4, the average difference in length between exposed and untreated twins was 0.2 centimeter. Both at birth and after 4 years, the average difference in length was less than 1 percent.

The mean difference in head circumference at birth between the exposed and untreated twins was 0.92 centimeter (table 7). On reexamination it was found that the mean difference in the head circumference between the exposed and untreated twins was 0.17 centimeter. Therefore, the slight difference in head circumference at birth was largely equalized after 4 years.

No eye damage was found in the 23 twin pairs at birth. All of the prematurely born infants were examined by an ophthalmologist before they were released. There was never any case of retinal damage.

Strabismus was seen in 5 out of 16 pairs of twins during the 1974 reexamination at the age of 4 years. Therefore, the proportion of paresis of the eye muscle was relatively high, namely, 30 percent. Since, however, in five pairs both twins showed the same symptoms, although only one of the five had been exposed, these cases of strabismus cannot be ascribed to phototherapy.[9, 24]

An intelligence test cannot be conducted accurately before the children have reached public school age. For this reason, we tested the general development of the children by means of the Bühler-Hetzer test.[23] In this test, a total of six parameters is examined, namely:

1. Sensory reception
2. Physical control
3. Social contact
4. Learning ability
5. Manual dexterity
6. Mental ability

The average value of the development quotient in the exposed twins was 0.9688. The average value in the untreated controls was 0.9635. In other words, these average values are approximately equal. There was a very slight difference in favor of the twins who had been subjected to phototherapy.

Parents reported that the social contact between the twins was extremely

TABLE 7. *Mean head circumference in identical twin sets with or without phototherapy*

Therapy	Head circumference at birth (centimeters)	Head circumference 4 years later (centimeters)
Light	31.72	50.33
Control	32.64	50.50
Difference	[1] 0.92	[2] 0.17

[1] 2.18 percent.
[2] 0.34 percent.

close. Any separation, even of a temporary nature, caused great difficulties. On the other hand, there was almost always a certain "order of precedence": the more active and quicker reacting of the twins was predominant.

Without any knowledge of the control groups, the majority of parents described the exposed, that is, the lighter weight of the twins, as predominant; the untreated twin was predominant only in five cases. In the unexposed comparative group, too, the same relation in favor of the "smaller" partner prevailed.

DISCUSSION

Monozygotic twins are obviously an excellent model for studying the effects of a single external factor, such as phototherapy, on a subject, since all genetic conditions are the same.[25] Photographic records at different ages were made of all twins studied. Dizygotic twins, on the other hand, can show very considerable variations.[26]

Even monozygotic twins are, strictly speaking, only very alike, but never identical, in the true sense of the word. That is why mothers can always differentiate between their monozygotic twins at first sight, fathers almost always, and strangers only with great difficulty or not at all. For example, we never found an identical pair of twins with exactly the same weight at birth. The difference in weight at birth in all 35 pairs of twins investigated by us was significant. The birth order (first or second) had no influence on the initial difference in weight.

As a matter of principle, we always treated the newborn with the lower birth weight when we carried out our comparative studies.

The weight increase of our twins during and after phototherapy, that is to say, in the first weeks of life, was relatively better than that of the untreated controls. This result contradicts the results obtained with young Gunn rats that had shown inhibited growth when exposed to light.[16]

Later, Ballowitz [27] found a different explanation for the inhibited growth of exposed Gunn rats. She interpreted the cause as decreased lactation output of the mother rats and decreased sucking ability of the young rats when exposed to blue light. When the young rats were artificially fed, no more adverse influence of phototherapy on the weight increase was observed.

All of our twins were artificially fed, using adapted milk administered via a permanent nasal tube. Both twins were given the same amount of food and fluid during the first week of life. Since, however, the exposed twin weighed on the average 8 percent less than the control twin, the exposed twins received slightly more food than the untreated controls (the amount of food being calculated on the body weight). This fact offers a sufficient explanation for the relatively better increase in weight of the exposed twins, as observed by us. Furthermore, we believe that a lower bilirubin load would also promote weight increase in premature infants.[5,27–29]

During our followup examinations in 1974, we were pleased to find that all of our subjects had developed normally, both mentally and physically. More specifically, they were in the median or lower range of their age group. This is fully consistent with the statistical results of large-scale surveys of premature infants and is therefore to be expected.[30]

A remarkable fact found during weight control was that the twins with the lower birth weight had been exposed to light practically always remained lighter than the controls. On the other hand, there was a distinct tendency to catch up.

When comparing the three somatic parameters: weight, height, and head circumference, it will be seen that the height has already leveled out, while a slight difference still remains in respect to weight and circumference of the head. The differences were small and within the statistical random range. One could ask, however, if this is not possibly an indication of growth retardation caused by phototherapy.

A search of the literature found studies that had followed the development of identical twins of significantly different birth weight of more than 25 percent. The study found that 8 1/2 years later, the smaller twin at birth was consistently lighter in weight than the other twin and their development of intelligence was also retarded.[28,31–33]

Birth-weight differences in identical twins of more than 25 percent, however, are extremely rare and explained by "parabiosis." Our twin sets had an average weight difference of only 8 percent. None of our twin sets showed "parabiotic syndrome." At the age of 4 years, there was no difference in mental development.

Furthermore we compared our 16 alternately light-exposed twin sets with 12 pairs of identical twins that were not subjected to phototherapy. All examinations in these 12 twin sets were the same. We found complete consistency of results. In each case, the twin lighter at birth showed less weight, length, and head circumference at the age of 5. We even found slightly larger differences in the group that was not subjected to phototherapy.

We conclude, therefore, that the consistent retardation in development is a general biological phenomenon that is not in any way related to phototherapy.

Finally, we compared the average weight increase of our 16 twin sets, that is to say, the difference between birth weight and weight after 4 years of age. By means of the variance analysis, we found that the difference in average weight increase was well within the bounds of statistical variation.[34] We concluded, therefore, that phototherapy did not cause growth retardation.

We have full confidence that phototherapy has a beneficial influence on hyperbilirubinemia in newborn infants.[35, 36] The questions of the committee on phototherapy [35] may be answered in the following manner: The committee recommended long-term effect studies. We have done such a study, using identical twins and found no detrimental long-term effects. These results are in full agreement with our clinical observations in more than 1,200 newborn infants treated with phototherapy. All the treated children have been examined several times after discharge from the hospital.

On the other hand, after 5 years' experience, I see no need for expensive irradiance-measuring equipment in the hospital. This equipment might be suitable for a research laboratory, not for routine work in a community hospital.

SUMMARY

In 1969 we started a "co-twin control study" in 23 prematurely born monozygotic twin sets: The lighter infant of each pair was subjected to continual phototherapy for 6 days. The heavier infant remained untreated. In all other respects therapeutic measures and care were the same in both twins. In 1974 we reexamined 16 of these monozygotic twin sets. We extended our studies to 12 monozygotic pairs of twins, neither of which had been exposed to light. Furthermore, seven twin sets were investigated, both children having been subjected to phototherapy. So a total of 35 identical twin sets was included in our reexaminations.

Due to the early onset of phototherapy at the first day of life, the serum bilirubin values remained extremely low and attained an average maximum value of only 4.1 mg% on the fourth day. The serum bilirubin level in the untreated controls was about twice as high. The exposed children attained their initial weight level earlier than the controls, and the relative weight increase was maintained during the following weeks.

In the long-term controls, 4 to 5 years later, practically all children had developed normally, mentally and physically, considering their premature birth. In comparing both groups of twins, treated with or without phototherapy, there was no recognizable difference in mental development (Bühler-Hetzer Test).

A remarkable catchup between both groups was observed in the parameters of weight, height, and head circumference. The average weight increase between treated and untreated children was equal. This finding was statistically significant. On the average, no damage caused by phototherapy could be observed.

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Recent Observations on Light and Neonatal Jaundice[a]

Jerold F. Lucey and Jean Hewitt

A great deal of research has gone into defining the optimal microenvironment of the newborn infant with respect to oxygen, humidity, temperature, and bacterial flora. Little attention has been paid to the infant's light environment. The reasons for this were largely emotional. We did not seriously consider the possibility that light could have any effects on the growing infant. This attitude is no longer tenable.

Recent studies indicate that light can produce the following effects:

- Lower levels of serum bilirubin due to photodegradation in tissues
- Increased excretion of unconjugated bilirubin in bile and stool
- Increased urine pigment excretion
- Increased skin blood flow
- Decreased gastrointestinal transit time
- Increased insensible water loss
- Transient skin rashes and pigmentation
- Increased bile acid turnover (adults)

We are now in the phase where we suspect light may have many effects. The recent demonstrations by Ostrow and Berry,[1] Lund and Jacobsen,[2] and Thaler et al.[3] in humans that light can increase the excretion of unconjugated bilirubin are extremely important. These observations will open up whole new areas of research on the effect of light on hepatic drug metabolism.

In this regard I would like to digress a moment to cite an interesting animal study we are now doing. Adult frogs were shown by Lester and Schmid[4] to have uridine diphosphate glucuronyl transferase in their livers but to excrete unconjugated bilirubin. Biliary excretion of bile pigment as a glucuronide did not occur. Levine et al.[5] have demonstrated that this

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animal has Y and Z proteins (ligardin) in the liver cell. This species has no circulating bilirubin in the serum.[4] In order to test our hypothesis that in this animal, light might effect the excretion of unconjugated bilirubin, we exposed frogs whose gall bladders were cannulated to alternative 5-hour dark and light periods. Bile flow rates did not change, but the excretion of unconjugated bilirubin (micrograms (μg) per/24 hours per kilo of frog weight) increased from 377 μg to 1401 μg (figure 1). We believe this animal will be useful in future studies to elucidate the mechanism of how light effects the excretion of unconjugated bilirubin. It seems unlikely that the creation of peripheral photoproducts in this species can occur, as there is no measurable bilirubin in the serum either before or after light exposure. Liver cell membrane damage does not seem a likely mechanism on the basis of light microscopy study.

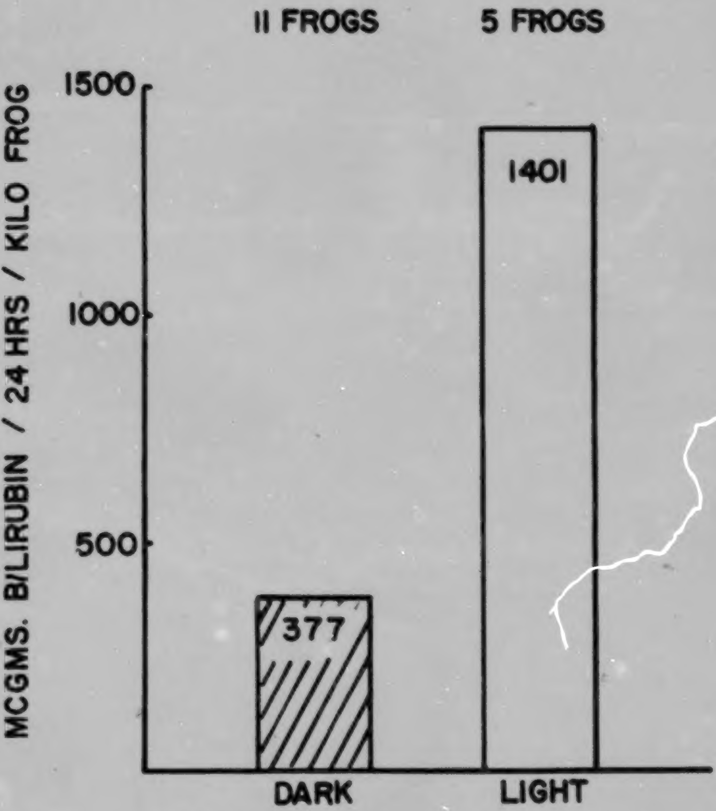

FIGURE 1. Average bilirubin excretion in the frog.

The present lighting conditions in our hospitals were not selected with any great care. It was assumed that if adequate light existed for adult personnel to see, then this would be a satisfactory environment for infants. Later some consideration was given to lighting that would enable physicians to visually assay jaundice and cyanosis. Little attention is still paid to the cyclical variation of light during the day and night. In many intensive care nurseries, windows have been eliminated, continuous artificial light is used, and small premature infants may not experience any natural sunlight for several weeks after birth. How do we know that this is correct? The answer, of course, is that we do not. It is assumed, by some workers, that our present lighting conditions are optimal and, therefore, deviations from present practice might be fraught with disaster. It is also assumed that "light therapy" is exposing infants to vastly increased amounts of radiant energy exposure. This is not always true. A good deal of misunderstanding exists on this point.

Let us examine what we do know about our present light conditions. MacLeod and Stern[6] have documented the well-known fact that great variations in light intensity of from 15 foot-candles to 2,500 foot-candles can occur. It has also been documented that a general level of 9[illegible] foot-candles in a nursery is effective in decreasing the incidence of hyperbilirubinemia.[7] The majority of "phototherapy" studies have been done using 200–400 foot-candles of broad spectrum light—an amount arbitrarily selected in 1958 by Cremer, Perryman, and Richards.[8]

The following factors are very important in assessing the present normal light environment:

- Sun and cloud formation
- Window location
- Season
- Clothing
- Type of incubator
- Feeding
- Environmental light
- Equipment on incubator
- Skin lotions
- Exposure angle—Reflecting surfaces

The infant lives in a rapidly changing sea of radiant energy of very variable intensities. We initially assumed that when we carried out our study in 1966[9] of the effects of light on serum bilirubin in premature infants that we had two groups—normal controls and a light-treated group. I would now challenge this assumption made by us and many others as a gross oversimplification of a difficult problem.

We have carried out careful studies over a 24-hour period in our nursery using a number of different spectroradiometers. These devices are more appropriate to use than light meters because they measure the amount of radiant energy in selected wavelengths—the irradiance in microwatts per square centimeter—instead of supplying an expression of the sensation of brightness as do light meters.

Figure 2 represents a schematic version of the type of radiant energy exposure (expressed as microwatts per square centimeter between 440–470 nanometers) that an infant receives in our nursery in a day if the incubator was near a window with an eastern exposure. One sees that this infant receives a high amount of total light exposure for a short period of the day as compared to the infant receiving lower but fairly continuous amounts of light exposure under conventional phototherapy. At different seasons, this exposure would obviously vary. This highly variable but potent source of light exposure has in the past been neglected, as no studies I am aware of have measured it in the control group.

Another way of expressing these data is to compare the 24-hour theoretical exposures received expressed either as irradiance (figure 3) or as dosage (joules) (figure 4). Whether expressed as irradiance or as dosage, it

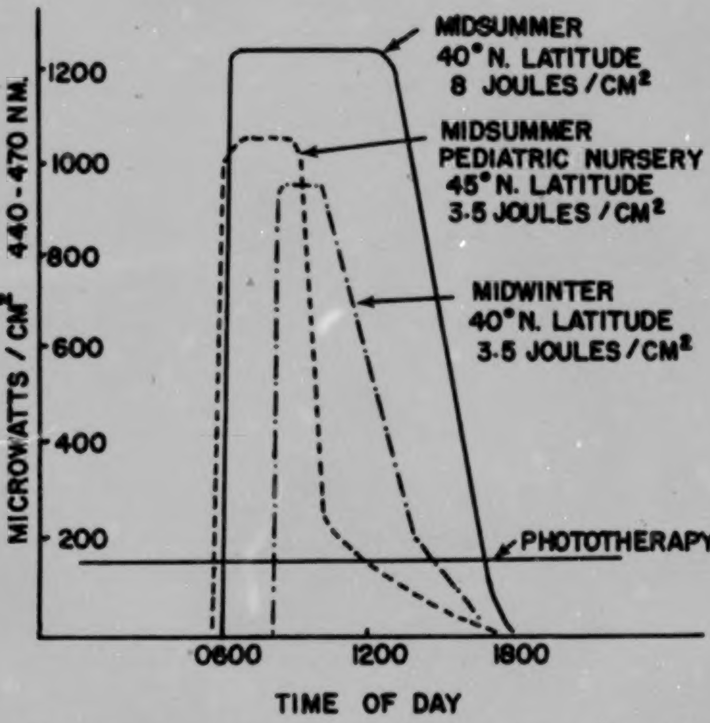

FIGURE 2. A flux day in the life of a premature infant in the nursery with windows.

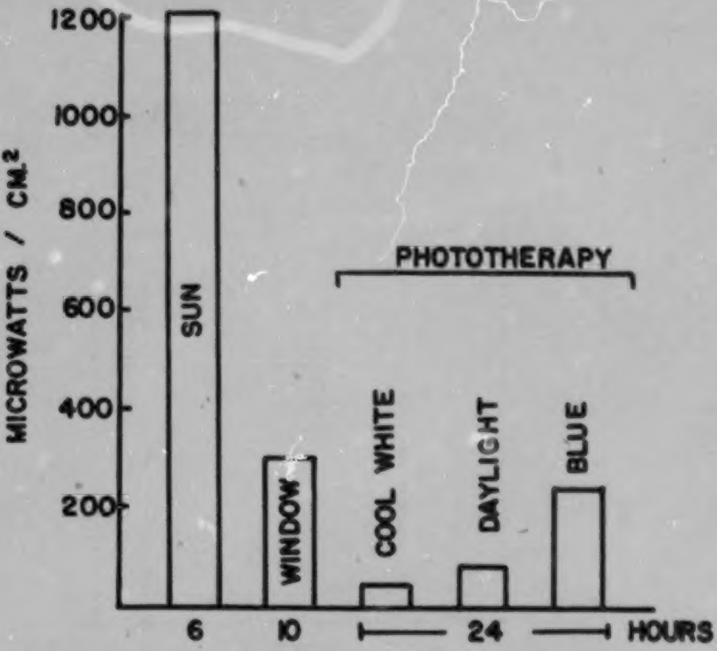

FIGURE 3. Light irradiance in the newborn nursery, 440–470 nanometers.

is obvious that at least in some nurseries the natural light exposure of an infant is an important variable.

We are suggesting that in the future one should perhaps compare the radiant energy exposure of these infants on the basis of a total 24-hour exposure period. The term "flux day," at various specific wavelengths, could then be used. This would allow more meaningful comparisons of light dosage than now exists. Looked at in this fashion, one sees that the infant near a window in Vermont for 6 hours can actually receive more radiant energy exposure in the 440–470 nanometer range than does the infant under conventional phototherapy with daylight bulbs for 24 hours. I appreciate that few infants are exposed to direct sunlight via a window, but in this comparison we have actually used levels of natural light intensity that are commonly achieved in some nurseries with windows.

The point we wish to make is that intermittent phototherapy has been going on in nurseries for years under uncontrolled conditions. This important point has been ignored. The value of studies where the light conditions of the controls have not been precisely defined must now be questioned. The repeated concerns expressed by some that so-called light therapy might be dangerous or highly experimental should be tempered by this consideration. There is no evidence available—other than tradition—that

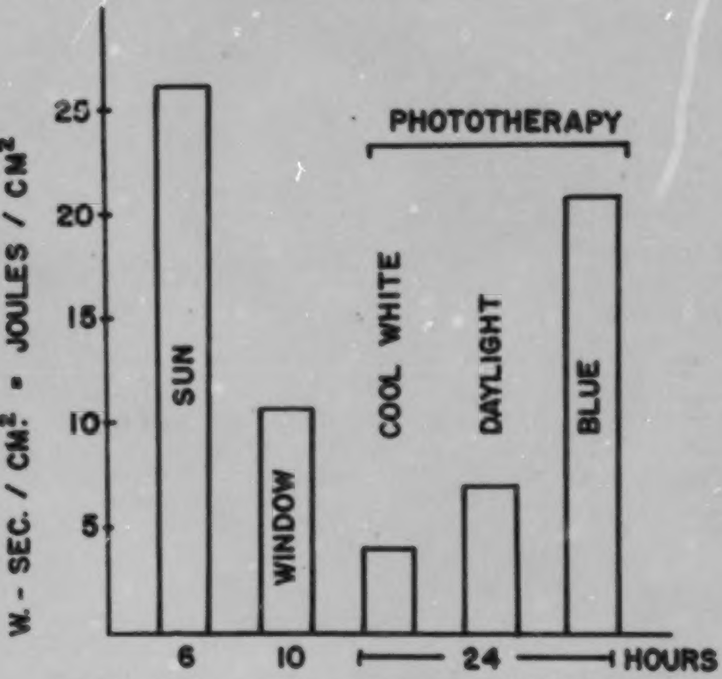

FIGURE 4. Light dosage in the newborn nursery, 440–470 nanometers.

establishes the present conditions as optimal. In fact, a good case can be made for the hypothesis that a component of neonatal jaundice is due to light deprivation. It would be but another example of our inability to correctly select, from adult standards, the best environment for the infant.

It will not be easy to select the correct amount of radiant energy exposure an infant should receive. As with all radiation, the least amount of exposure that will accomplish the desired effect seems to be the best goal. On the basis of animal studies in the Gunn rat,[10] we estimate that to be effective in lowering serum bilirubin, a light must supply at least 100 microwatts per square centimeter at 440–470 nanometers. Present phototherapy units usually supply much more than this.

A number of important variables keep us from applying this figure to humans. The skin is one such variable. Its thickness obviously varies with gestational age and area of the body.

The amount of light that will penetrate in these areas is obviously different. No studies of this important point have been carried out.

The exact site of action of light is still not known. In future calculations of light dosage, the area exposed, skin thickness, and penetration will all have to be considered.

If an important side of action is intravascular, another factor that may be important is the hematocrit. This has been suggested by Blackburn and Orzalesi.[11] In the in-vitro study (figure 5), we compared the effects on a solution of bilirubin in serum in which the only variable was the hematocrit. All samples were agitated constantly during the 24-hour light exposure. The blood with a high hematocrit had less of a fall in bilirubin concentration than the low hematocrit blood. In a clinical situation, this may be a contributing factor to the differences in response of serum bilirubin to light that one observes in different infants.

We have carried out a few postmortem studies on the relative penetration of light through the newborn scalp and skull bones. Simple proof that light penetrates the skull is supplied by the well-known use of light for transillumination of infants[2] heads in the nursery. In this study (figure 6), an Instrument Specialties Co. spectroradiometer cosine-corrected probe was placed within the empty cranium of two prematurely born infants at postmortem examination. The light source tested was a standard Air Shields phototherapy unit equipped with six daylight fluorescent tubes. In each study a small percentage of the incident light at wavelengths 490–520 nanometers penetrated the skull. It is important to note that wavelengths commonly used for heating had great penetration. No studies of the effects of this common widespread use of radiant energy have been carried out.

We have recently reviewed our clinical experience with the use of phototherapy ("supplemental light") in low-birth-weight infants for "physiologic jaundice of prematurity," and mild ABO or Rh blood group incompatibility, in the presupplemental light era (1960–66) of our nursery and in the

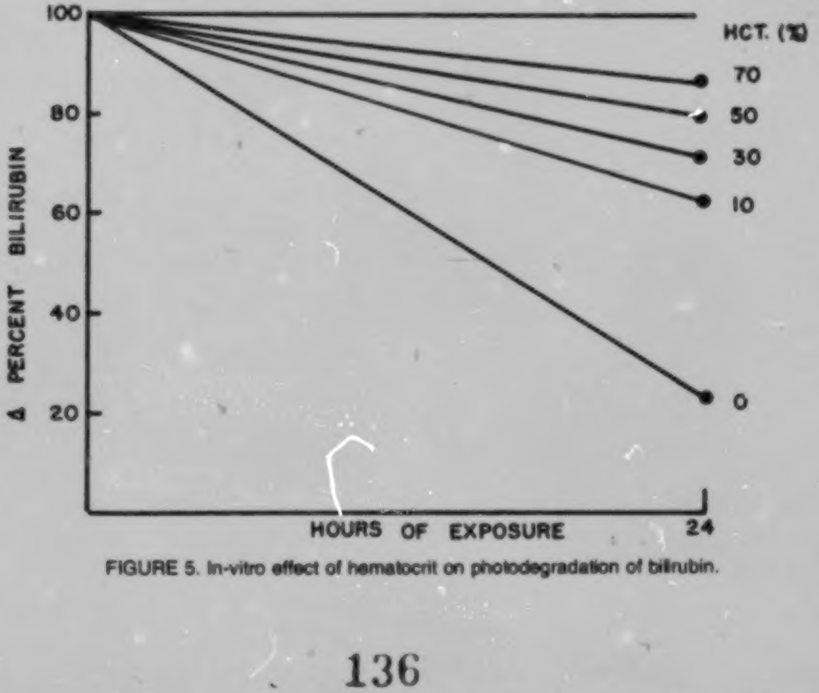

FIGURE 5. In-vitro effect of hematocrit on photodegradation of bilirubin.

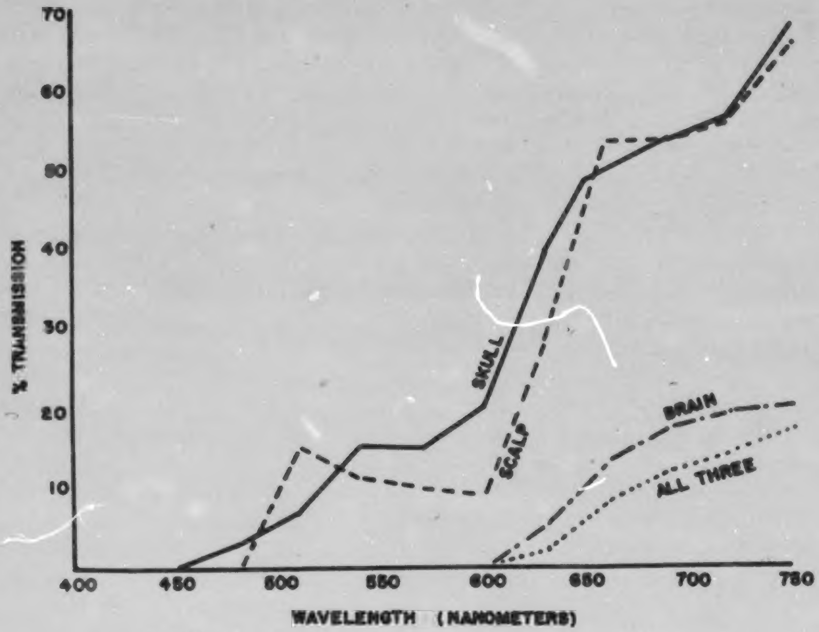

FIGURE 6. Light penetration—skull of 1,500-gram infant.

period when we have been using "more light" in the nursery environment (1967–73). In 1960–66 we had 949 low-birth-weight (less than 2,500 grams) infants admitted to our unit. We performed serum bilirubins on 60 percent of these infants, and 14 percent were found to have serum bilirubin concentrations of over 15 milligrams percent (mg%).

During the next 6-year period 1967–73, we had 870 infants admitted. During this era we were using increased amounts of environmental lighting in a variety of ways. We treated 47 percent of these infants with light. We did serum bilirubin studies on 60 percent of the total infants admitted. We found that 4 percent developed serum concentrations of over 15 mg% (see table 1).

An analysis of our recent experience indicates that we tend to be using light on a higher percentage of infants in 1972–73 and doing more serum bilirubins, but that the incidence of hyperbilirubinemia, defined as a serum bilirubin of greater than 15 mg%, has not changed appreciably. The significance, if any, of this is difficult to interpret because since 1972 we have experienced an increased number of infants being transferred from other hospitals with severe respiratory distress and other illnesses. These are factors that would tend to increase the incidence of hyperbilirubinemia.

The only conclusions we draw from looking back at this experience is that one can significantly decrease, but not eliminate, hyperbilirubinemia in

TABLE 1. *Phototherapy experience, Low-birth-weight infants, 1967–73*

Year	No. of infants [1]	Light therapy	Bilirubins done	Serum bilirubins		
				<10	10–15	>15
		Percent				
1967–68	156	33	54	69	25	5
1968–69	135	47	47	73	20	6
1969–70	192	44	52	63	33	4
1970–71	140	47	65	45	52	3
1971–72	130	47	58	61	35	4
1972–73	117	71	84	43	53	3
Average		47	59	59	36	4

[1] Total number of infants is 870.

such a population of infants by the use of phototherapy or "supplemental light" in approximately one-half of the infants. We have not had a low-birth-weight infant with a serum bilirubin of over 20 mg% in the last 9 years as of July 1, 1976. We have not had any cases of kernicterus at postmortem examination, and we have not observed any clinically during the last 12 years. We make no claim that our experience can answer the important question of whether the incidence of "low bilirubin kernicterus" can be changed by phototherapy. Our experience combined with others is, however, most reassuring in that there is no evidence that neurologic damage is occurring in treated infants. If a "kernicterus like" picture were going to show up due to a change in say bilirubin binding capacity of serum albumin, as has been hypothesized, it would be apparent by now, as the clinical experience in the United States and the world is now of 15 years' duration and involves thousands of infants. None of the speakers at this symposium has observed any unusual increase in the incidence of neurologic damage thought to be due to bilirubin; in fact, a decreased incidence of kernicterus at postmortem examination has been reported by Ploussard.

We have carefully followed up 99 infants (55 controls and 44 light treated) of our original study carried out in 1966.[12] These infants have been seen by a pediatric neurologist. They have had psychometric evaluation and speech and hearing evaluation, all carried out by examiners who did not know the status of the child at the time of the study.

We failed to detect any significant differences in these two groups in IQ, speech and hearing, neurologic status, or head circumference (table 2).

The whole question of an effect, if any, on head circumference and IQ of phototherapy is going to be an exceedingly difficult one on which to do a control study. The basic reason for this is that we of course do not know, nor can we control, the important factors (genetic and environmental—both pre- and postnatal, calories, and viral infections) that are known to have very profound effects on these parameters.

A question has also been raised as to the possible effect of light on serum

TABLE 2. *Results of a 6-year followup in 1972–73 of a controlled study of 99 low-birth-weight infants treated with phototherapy in 1966*

Group	No. of infants	Average weight (grams)	Head Circumference		Psychometric		Hearing		Neurologic	
			N	S	N	A	N	A	N	A
Control	44	2,134	43	1	30	10	40	8	34	2
Light	55	2,072	48	5	22	9	31	6	46	3

Note.—N = normal, S = small, A = abnormal.

free fatty acid concentrations. Figure 7 summarizes our experience on this point. We were unable to detect any difference on the second, fourth, or sixth day of life when the light group was compared to controls. These were the infants in our original study.[9] We have not published these observations previously. We were also not able to detect any difference in serum leucine amino peptidase values (figure 8). This was reassuring to us, as this test is a sensitive index of biliary tract damage.

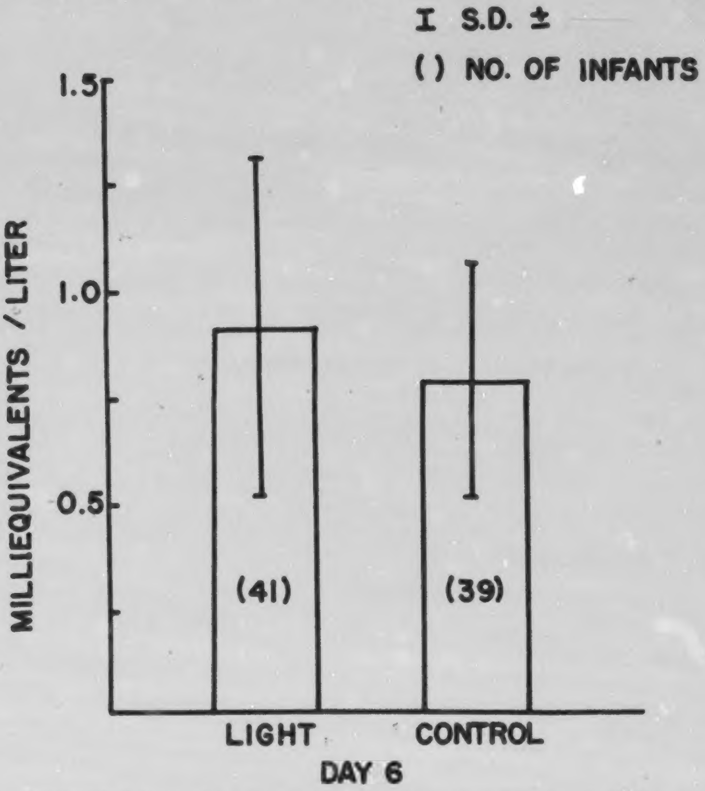

FIGURE 7. Serum free fatty acid values—phototherapy and control infants.

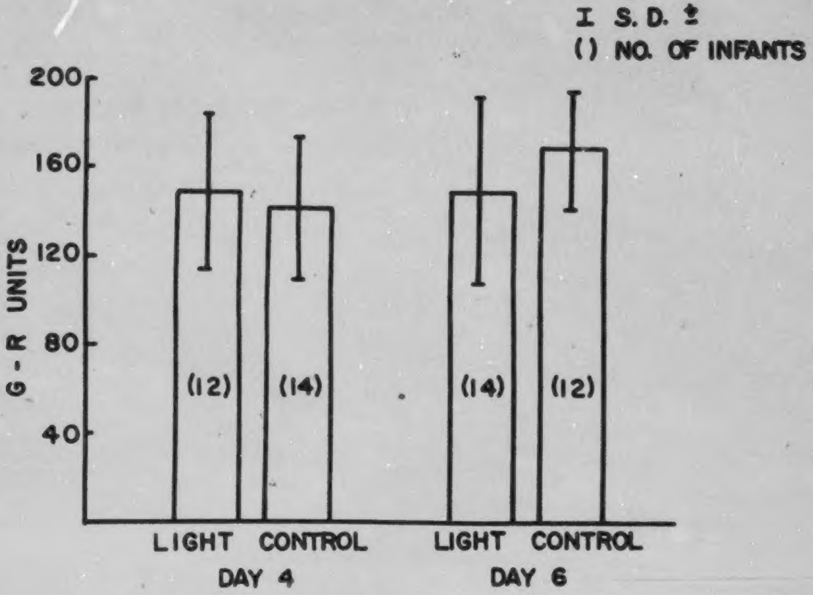

FIGURE 8. Serum leucine amino peptidase values—phototherapy and control infants.

SUMMARY

We have called attention to how little is still known about the light environment of the infant. We challenge the assumption that present conditions are either optimal or inviolate. If one accepts our concept of a flux day, normal infants in many nurseries can receive as much or more radiant energy exposure than is being received by infants under phototherapy. We also suggest that in the future the flux day concept be used for reporting. In future attempts to define the correct light dosage, consideration must be given to such factors as skin thickness, area and penetration, hematocrit, and the penetration by light of different wavelengths.

Controlled clinical studies in which the light conditions of the normal controls are not more precisely defined will be very difficult if not impossible to interpret.

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Discussion

Dr. Ostrow: How do you know that the pigment you measured in the frogs was unconjugated bilirubin?

Dr. Lucey: It is diazo-positive material. I would really like to see some of the professional bilirubin people get interested in this particular model to identify the products. We could not measure any bilirubin in the serum. Neither could Drs. Schmid and Lester years ago. This may mean that there is some fairly deep effect of light on the liver.

Dr. Gartner: I am troubled that if there is no bilirubin in the circulating blood or in tissues and yet you get a marked increase in excretion, then presumably, the effect of phototherapy might be to increase bilirubin production in the liver.

Dr. Lucey: That is one possible interpretation.

Dr. Schmid: The frog is really quite different from the mammal. We got interested in it because E. B. Brodie in the middle 1950's, had shown that amphibia develop conjugating mechanisms only on metamorphosis. Just by chance we looked at the tadpole. It turned out that the tadpole has icteric serum, in which bilirubin can be measured by conventional methods. This was interesting because the frog has no bilirubinemia and has a functioning conjugating mechanism, yet bilirubin in the bile is not excreted as the glucuronoside.

There are several facts to be remembered. First, there is practically nothing in the serum that resembles albumin, so there is no carrier protein to speak of in the frog. If one injects a frog intravenously with bilirubin, it disappears very rapidly from the circulation and gets into the liver, and it sits in the liver for a long period of time. The excretion in the bile is very slow. It is an extremely sluggish process. What appears in the bile is largely pigment released gradually from the liver. The similarity with the unconjugated bilirubin excretion in the human infant or the Gunn rat under light treatment is striking. This must mean that the light does something that eventually changes the secretory mechanisms of the liver but what this is, is an open question.

Dr. Ostrow: How can you say that the light does not alter the composition of the bilirubin in some way?

Dr. Schmid: One of the possible explanations is that the bilirubin in the skin in some way is modified by the light so that the liver no longer needs conjugation for excretion. I find it hard to believe that the liver itself would get sufficient light to affect its secretory mechanism.

Dr. Hastings: You are suggesting that this effect is due to direct absorption of bilirubin by the liver in light?

Dr. Schmid: One would have to assume that something either gets hooked on, or complexes with, the bilirubin so that it is carried through the liver, but the liver does not recognize it as bilirubin, and it falls apart again after secretion in the bile.

Dr. Hastings: Maybe it is a bilirubin X complex and it breaks that bilirubin bond? Is it a direct light effect when you turn the light on? The total amount excreted during the light and the total amount excreted during the dark is shown.

Dr. Lucey: This is the same animal during 5 hours of light period and during 5 hours of dark period. You have a dark collection period and then we turn on the light and have a light collection period.

Dr. Hastings: Could the changes observed be due to an altered circadian rhythm?

Dr. Lucey: That is a possibility. We have not looked into it. Also, nobody seems to know very much about what changes occur in liver functions during hibernation. There must be some fairly profound changes. There is still a possibility that the light activates something in the skin, which is then attached to bilirubin.

Dr. Schmid: Dr. Karabus, why were so many more male babies admitted to your hospital than female?

Dr. Karabus: I do not know. Male babies are more affected by jaundice than girl babies.

Dr. McDonagh: There was no difference in the long-term followup between the twins. Doesn't the experiment show that it is not worth giving phototherapy treatment for bilirubins as low as these?

Dr. Friederiszick: We treated 62 percent of our underweight premature children, and we started very early. We are not afraid to speak of prevention of hyperbilirubinemia.

Dr. Karabus: Doctor, your study was a beautiful one, and should put a lot of people's fear to rest. I think that possibly one criticism of it is that you have not really eliminated the possibility that degradation of bilirubin could cause harm, because your babies really never had very much bilirubin to be degraded.

What you have really shown is that there is no harmful effect of the light itself. The bilirubin never rose higher than 12 milligrams percent. There was really very little photodegradation product that could possibly cause damage.

Dr. Friederiszick: We think there is no harm from light. I think that it is the best way to prevent hyperbilirubinemia.

Dr. Karabus: Not many people are going to use phototherapy therapeutically in babies whose bilirubin is below 8 milligrams percent.

Dr. Zuelzer: You may be surprised when this conference is over.

Dr. Karabus: What I am trying to say is that what has not been shown is the effect of phototherapy on a bilirubin level of 15 milligrams percent. This has not been eliminated by the study.

Dr. Johnson: I agree. I think that with this study we can be reassured only that in infants with serum bilirubin concentrations of 12 milligrams percent or less, light is safe.

Dr. Lucey: I wish I could pick out a level and say that we maintain rigid control. I cannot make that claim. A suggested level over the past few years has been to start phototherapy at 10 milligrams percent. It is very difficult to enforce that kind of rule if you are not around constantly.

Dr. Zuelzer: We have heard some pretty convincing studies about the preventability of hyperbilirubinemia and the harmlessness of light per se. What are we going to take back? I would like to address this question to a number of people here. The risk of kernicterus in babies who have respiratory distress syndromes, hypoxia, hypoglycemia, acidosis, etc., is high. We have been talking here mostly about relatively normal premature infants. What can or should you do about that? The level at which exchange transfusions are being given now is creeping down steadily. Cases are being cited with 12, or even 8, milligrams that are associated with kernicterus. Do we have enough information to ask the question? Are those levels in the presence of or controlled by phototherapy going to be less risky?

Dr. Lucey: We do need some type of study along the lines of the one that the National Institutes of Health plan to do.

Dr. Zuelzer: It may be that we will not be able to detect the difference between the two groups unless a large number of infants are involved. The larger the number, the longer the time and the greater the cost. It seems to me like a very long hard road that we have ahead of us.

Dr. Johnson: Is your question that the proposed level for doing exchange transfusions is so low that it is going to take a long time to find any damage in untreated infants?

Dr. Gartner: That is one of the questions.

Dr. Johnson: The protocol says that a baby weighing between 1,000 and 1,500 grams who falls into the "no-phototherapy" group will be allowed to develop 15 milligrams percent of hyperbilirubinemia before any treatment is instituted, and that if that infant is sick, even very sick, treatment for jaundice will be withheld until a level of 13 milligrams percent is exceeded. I think that is very high. Haven't you found that most vigorous 1,250-gram prematures with a serum bilirubin concentration of 15 milligrams percent and, in particular, most sick 1,250-gram prematures with serum bilirubin concentrations of 13 milligrams percent have binding studies in the danger range?

Dr. Gartner: We are now doing four different binding studies on all infants. The interpretation of "danger range" awaits more data and followup studies. These infants have many reasons for not doing well, and some may or may not alter the risk of bilirubin-related brain damage. It is possible to argue either that these levels are too high or place the infant at too great a risk from kernicterus, or that they are too low and place the infant at too great a risk from exchange transfusion. Both of these points of view have been presented today in criticism of the controlled clinical trial of phototherapy. I believe the levels chosen are as safe as present knowledge allows and thread the fine line between the two more extreme positions. The performance of a large study of phototherapy as a controlled clinical trial is essential if we are going to be able to prove both the effectiveness of phototherapy in preventing kernicterus and the safety of the procedure. I believe the effort and cost are justified.

Dr. Tan: If you lower the level of 15 milligrams percent, all my infants would have to be exchanged, because nearly all my infants have over 15 milligrams percent.

Dr. Johnson: But you are not treating them with very much light.

Dr. Tan: I find that all my infants, even after 18 milligrams percent, do very well developmentally.

Dr. Johnson: We are not talking about just growth.

Dr. Tan: We feel in Singapore that we can pick up early signs of brain damage. Maybe it is because of the vast experience we have.

Dr. Ostrow: I would like to make a comment and to tell a story. A small boy is walking along a Vermont road with a fishing pole. A car drives up and the lady asks, "Little boy, is this the route to Burlington?" He replies, "I don't know." "Well, does Route 5 go to Burlington?" He says "I don't know that either, ma'am." "Little boy, you are not very bright are you?" "Maybe so," he replies, "but I'm not lost."

The point I am making is that everybody has a conviction or a feeling as to how light should be used. Some are using it prophylactically; Dr. Odell does not use it at all. This illustrates that we feel that we are not lost, but we really do not have the data necessary to make that decision. I would like to suggest for the long-term study that both of the relatively extreme views be used: one that you ought to use phototherapy at low levels or treat prophylactically, and the other that phototherapy should not be used at all. As long as you do not have the data to choose one or the other view, the group cannot possibly come to a valid consensus. Let us include both extreme views in the study and find out once and for all where we are.

Dr. Odell: I am not questioning what you are saying. I am just worried that one might take away the message that we can prevent bilirubin kernicterus in low-birth-weight infants when it was not kernicterus at all; it was yellow staining of necrotic neurones previously damaged by hypoxia.

Dr. Landes: Suppose you have a baby who is premature, distressed, and jaundiced, and dies because of respiratory problems. At autopsy if the brain is sectioned one sees some yellow staining. Did that infant have kernicterus or did he have yellow staining and no gross clinical evidence of kernicterus?

Dr. Zuelzer: If there is no hemorrhage associated with it, I would have to call that kernicterus.

Pathobiology: Basic and Clinical Considerations

Photosensitivity Diseases: Role of Electromagnetic Radiation [a]

Leonard C. Harber and David R. Bickers

Rapid advances in knowledge concerning the role of solar radiation or "light" in health and disease have occurred during the past decade. This has paralleled similar advances in two basic science disciplines: photobiology and photochemistry. Accordingly, many photosensitivity diseases that predominantly affect the skin and were previously poorly understood as to mechanism can now be described in detail with the aid of diagnostically useful biochemical and biophysical information.

Solar radiation, in general, elicits many responses including warmth, vision, and sunburn. Of greatest importance, however, is the photochemical process known as photosynthesis through which solar energy is converted into a form of chemical energy that can be used by animals and man for metabolic processes critical for growth, development, and homeostasis.

The green heme-pigment chlorophyll selectively absorbs light in the visible wavelength range and acts as a solar energy trap. The absorbed light is then converted by photosynthesis into energy-rich carbohydrates, a form of energy that is ingested by animals and converted into energy-rich proteins, fats, and carbohydrates. These, in turn, are consumed by man and provide him with the fuel for his metabolic requirements. It should be noted that the fossil fuels used for heat and power on the earth today also originated from vegetable sources.[b]

The purpose of this report is to review selected aspects of radiation physics pertinent to light-induced disorders in man and then to stress selected photosensitivity diseases that could potentially pose a hazard as a result of phototherapy. These remarks are intended solely as a framework in which to discuss selected photosensitivity diseases in man.

CHARACTERISTICS OF THE ELECTROMAGNETIC SPECTRUM

Solar radiation reaching the earth's surface may most conveniently be defined in terms of wavelength. The units of wavelength include angstroms

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[b] A minimal amount is presently obtained from nuclear fission.

(Å) (10^{-10} meters) and millimicron (mμ), or nanometer (nm) (10^{-8} meters). The latter is presently the most widely advocated and will be used here. Solar radiation in the 400- through 800-nm range is absorbed by the ocular photoreceptors of the retina and, following their excitation, is perceived as visible light. Wavelengths below 400 nm reaching the earth are known as ultraviolet and extend from 290 to 400 nm. Those wavelengths extending beyond the upper limit of visible light (800 nm) are known as infrared or heat waves, and such wavelengths range between 800 and 4,000 nm.

It is convenient for the understanding of selected photochemical phenomena to discuss light in terms of quanta or photons. According to quantum theory, solar energy is transmitted as discrete packets called quanta or photons. The energy of a single photon has been related to the wavelength of light by the now-classic studies of Planck and Einstein and expressed by the formula $E = \frac{hv}{C}$, where E is the energy of a single photon in ergs; h is Planck's constant, 6.62×10^{-27} erg seconds; C is the velocity of light, 3×10^{-10} centimeters per second; and v is the frequency of the radiation per second. The energy of a single photon is so small that in practice one usually refers to the energy of a mole of photons known as an Einstein. The effects of photons or quanta on biologic systems rests firmly on two fundamental principles:

1. The Grotthus-Draper law or first law of photochemistry: This axiom states that before any photochemical reaction can occur light must be absorbed by a molecule.
2. The Stark-Einstein law or second law of photochemistry: This axiom states that only one photon is required to excite a given molecule after absorption.

Inherent in these laws is the concept that specific compounds will absorb only specific wavelengths of light as indicated by molecular configuration and as reflected by their absorption spectrum. The energy that this represents is the amount exactly equal to that required to permit the molecule to reach a so called "allowed" excited state. The biologic responses evoked by light are all wavelength dependent. A plot of the biologic or chemical response as a function of wavelength is called the action spectrum for that response. Accordingly, by measuring the in-vitro absorption spectrum of a chemical, one can estimate the wavelengths of light that can produce a photochemical effect following excitation. In contrast, the absorption spectrum simply refers to the range of wavelengths that a given chemical or biologic system can absorb.

PHOTOSENSITIVITY DISEASES

The recognition of cutaneous diseases in which sunlight is thought to play an etiologic role has expanded considerably in recent years. The scope of these disorders is such that stringent classification is not easily accomplished. Table 1 contains an arbitrary classification of photosensitivity diseases, based on etiology, divided into five categories. The table is presented solely as a framework for discussion of selected disorders in man. In each of the diseases presented in the table, an approximate action spectrum range is noted. In general, they are divided into two groups. The first group comprises diseases due to the 290 to 315-nm range and appear causally unrelated to presently known effects of phototherapy in hyperbilirubinemia. The second group encompasses diseases due to wavelengths extending from 380 through the visible light spectrum and includes all categories except degenerative and neoplastic. This action spectra range includes those wavelengths presumed to be emitted by light sources used in the phototherapy of hyperbilirubinemic infants. These light sources have an emission spectrum extending from 380 to 800 nm.

TABLE 1. *Classification of photosensitivity diseases*

Item	Range of effective wavelengths (nanometers)
I. Genetic and metabolic:	
Xeroderma pigmentosum	290–315
Erythropoietic protoporphyria	390–420
Erythropoietic porphyria	390–420
Porphyria cutanea tarda	390–420
Albinism	290–315
II. Phototoxic and photoimmunologic:	
a. Phototoxic:	
Internal (drugs)	290–800
External (drugs, plants, fruits)	290–800
b. Photoallergic:	
Solar urticaria [1] (immediate hypersensitivity)	320–800
Drug photoallergy (delayed hypersensitivity)	320–450
III. Degenerative and neoplastic:	
Chronic actinic skin damage	290–315
Actinic keratosis	290–315
Basal cell epithelioma	290–315
Squamous cell carcinoma	290–315
Malignant melanoma (?)	290–315
IV. Miscellaneous:	
Hydroa aestivale	290–315
Hydroa vacciniforme	290–315
Polymorphous light eruption	290–500
Polyvalent light sensitivity	290–800
V. Photoaggravated:	
Discoid lupus erythematosus	290–315
Systemic lupus erythematosus	290–315
Dermatomyositis	290–315
Herpes simplex	290–315
Darier's disease	290–315
Bloom's disease	290–315

[1] Only one of six types is definitely immunologic.

Genetic or Metabolic

Xeroderma pigmentosum is an autosomal recessive disorder characterized by the development of numerous cutaneous malignancies during the first 2 decades of life. Many of these individuals die at an early age with extensive metastases from these cutaneous tumors. Patients with xeroderma pigmentosum appear to have a specific metabolic defect that may explain their unusual predilection for skin tumors. Normally, ultraviolet light produces specific structural alterations in DNA known as thymine dimers. The action spectra appears to be in the 250-to 315-nm range. This light-induced cross-linking of DNA is repaired by enzyme activity in normal individuals, but such enzymes appear to be deficient in patients with xeroderma pigmentosum. In selected cases, it would appear that there is deficient activity of an endonuclease that leads to faulty excision of the damaged thymine dimer portion of the DNA molecule [1] The precise manner in which this repair defect leads to malignancy has not been defined. The fact that a structural derangement of DNA can be associated with cutaneous malignant change is an exciting one that is currently under intensive investigation in several laboratories. Actually, there is very little emission of 290- to 315-nm radiation by light sources used in phototherapy, but the exquisite sensitivity of the skin in these patients may render them susceptible to skin damage by phototherapy.

Porphyrias

The diseases known as the porphyrias result from specific defects in the porphyrin-heme biosynthetic pathway and lead to the accumulation of biochemical intermediates known as porphyrins within the body. The heme pathway is most active in the bone marrow and liver; hence the porphyrias are usually classified as either erythropoietic or hepatic. The porphyrins, regardless of their tissue of origin, are fluorescent compounds that absorb light intensely around 400 nm, the so-called Soret band. It is this absorption of light energy and its ultimate dissipation within living cells that apparently leads to tissue damage. Each of the porphyrias has characteristic clinical and biochemical features that now permit fairly definitive classification of patients with these disorders.[2]

Erythropoietic protoporphyria is an autosomal dominant disease that usually begins in early childhood. Affected individuals complain of "burning" and "stinging" in their skin shortly after light exposure and often manifest edema and mild eczematous changes on the face and hands (light-exposed body areas). The excessive porphyrin production originates in the bone marrow and is protoporphyrin. This water-insoluble compound is not found in the urine but is present in excess and is readily detectable in red blood cells, feces, or plasma.[3]

Erythropoietic porphyria is an extremely rare autosomal recessive disorder characterized by a mutilating photosensitivity, splenomegaly, and hemolytic anemia. These patients may die at an early age. Uroporphyrin I is produced in excess within red blood cells and appears to be the basic metabolic abnormality in these patients. The water-soluble uroporphyrin I is markedly elevated in red blood cells, plasma, and urine of these individuals.[4]

Porphyria cutanea tarda is the most frequently encountered clinical porphyria and is of uncertain genetic origin. These patients are usually of middle age and often have a history of moderate to heavy alcoholic intake.[5] This type of porphyria has been induced or exacerbated by many chemicals, some of which are noted in group III of table 2.[6] Porphyria cutanea tarda is a hepatic porphyria, the etiology of which remains unknown. Liver biopsy specimens demonstrate increased levels of uroporphyrin, predominantly uroporphyrin I, as does the urine. Clinically, these patients manifest large blisters, or bullae, erosions, and scarring on light-exposed areas, particularly the dorsal aspect of the hands.[7] In addition, increased skin fragility, facial hypertrichosis and hyperpigmentation are important components of the clinical syndrome.

Twenty-four hour urine porphyrin determinations are a simple and

TABLE 2. *Drugs associated with induction or exacerbation of cutaneous photosensitivity in man*

Item
I. Drug phototoxicity:
Sulfonamides
Sulfonylureas
Chlorothiazides
Phenothiazines
Tetracyclines
Psoralens
Coal tar:
Anthracene
Pyridine
Acridine
Phenanthrene
II. Drug photoallergy (delayed hypersensitivity type):
Halogenated salicylanilides and related compounds
Sulfonamides
Griseofulvin
Fenticlor
Multifungin
Jadit
Promethazine (Phenergan)
Thiazides
Tolbutamide (Orinase)
Chlorpropamide (Diabinese)
Substituted benzoic acids
Chlorpromazine (Thorazine)
Chlordiazepoxide (Librium)
III. Drug-induced porphyria:
Ethyl alcohol
Hexachlorobenzenes
Di- and trichlorophenols
Stilbestrol and other estrogens
IV. Drug-induced lupus erythematosus:
Procainamide
Hydralazine
Penicillin
Sulfonamides
Tetracycline
Streptomycin
P-aminosalicylic acid
Phenylbutazone
Methylthiouracil
Propylthiouracil
Reserpine
Isonicotinic hydrazide
Alpha Methyldopa
Oral contraceptives
Trimethadone
Methylphenylethylhydantoin
Diphenylhydantoin
V. Drug-induced pellagralike eruption:
Isoniazid
6-Mercaptopurine
5-Fluorouracil

accurate method to confirm a suspected diagnosis of porphyria cutanea tarda. The treatment of choice is phlebotomy, which often leads to prolonged remission of the clinical symptoms as well as the biochemical abnormalities as detected by porphyrin excretion. The porphyrias comprise a group of photosensitivity diseases that are exacerbated by light of 400 nm. Since there is substantial emission of such radiation by light sources used in phototherapy, care should be taken to see that there is no family history of porphyria in infants to be irradiated.

Albinism is an autosomal recessive disorder and is characterized by lack of skin pigmentation and usually severe photosensitivity due to a deficient production of melanin. The specific enzymatic aberration has not been defined but is related to decreased activity of tyrosinase. The end result, however, is a drastic reduction in the amount of melanin synthesized by melanocytes. The albino is biologically deficient in a molecule that is an excellent absorber, blocker, and scatterer of ultraviolet radiation.[8] Hence, these patients are much more susceptible to sunburn and cutaneous neoplasms. The diagnosis is made on the clinical appearance of the patients, which includes hypopigmentation of skin and the eye, with extreme photophobia and nystagamus.

Phototoxic and Photoimmunologic

Adverse reactions following consecutive exposure to selected chemicals and light were well defined by Raab[9] and others in the early 1900's. Since that time hundreds of chemicals have been demonstrated to produce cell damage in selected biologic systems after light exposure.[10]

The term "drug-induced photosensitivity" has been widely used in clinical medicine to describe adverse cutaneous reactions in man that follow the use of certain photosensitizing chemicals. Historically, the term "drug" was correct since known photosensitizing reactions had occurred following the administration of therapeutic agents to the patient. It was only following wide use of preparations that it became clear that exposure to these compounds followed by light could produce adverse reactions. With expanding medical knowledge, the general term "drug photosensitivity" has been enlarged to describe reaction patterns related to exposure to a broad group of chemicals used for many nonmedical purposes as well. These may be found in a wide range of compounds, including cosmetics, food preservatives, household cleaners, industrial products and byproducts, and agricultural items.

Two distinctly different mechanisms have been defined that can mediate these reactions in man. They are designated phototoxic and photoimmunologic. Selected disorders and the chemicals inducing such photoreaction are listed as headings in table 2.

It should be pointed out that as yet no such reactions have been reported in infants undergoing phototherapy. However, by careful monitoring of the drug history of the mother and the transplacental circulation of selected drugs, it may be possible to ascertain whether such reactions do occur. Such studies are now in progress by our group.

Degenerative and Neoplastic

As early as 1874, Unna [11] observed in German sailors exposed to sunlight for years degenerative skin lesions that we now recognize as actinic keratoses. In addition, he described carcinomas of both the basal cell and squamous cell types in these individuals. The lesions were confined to the light-exposed areas, and he correctly speculated that they might possibly be related to the excessive sun exposure of the seamen.[11] Since that time, numerous other agents have been identified that enhance formation of skin cancer in man. These include ingestion of arsenic,[12] exposure to ionizing radiation,[13] certain chronic infections such as lupus vulgaris and burn scars,[14] and selected genodermatoses.[1] These conditions, however, are rather unusual and comprise only a small percentage of the 250,000 skin tumors annually reported in the United States. Of these, at least 95 percent occur on the light-exposed areas of the body, and the overwhelming majority are associated with a history of excessive sunlight exposure. Those populations at greatest risk for solar skin damage are the blue-eyed, fair-complected Caucasian group with smaller amounts of melanin pigmentation. Experimental studies in mice as early as 1928 [15] indicated that tumors could be induced by ultraviolet light. By 1940, Blum [16] demonstrated that it was primarily the ultraviolet wavelengths below 315 nm that were carcinogenic.

Recently, studies by Willis, Kligman, and Epstein [17] have suggested that longer wavelengths of ultraviolet light may also have significant carcinogenic properties in that they are capable of causing DNA damage analogous to that induced by the sunburn spectrum (290-315 nm). If this is confirmed, it may be necessary to reconsider the action spectrum for neoplasia following light exposure. To date, there is no reason to incriminate phototherapy as a factor in degenerative and neoplastic disease. Recent, more accurate measurements of the emission spectra of lights used in phototherapy indicate that there may be trace amounts of ultraviolet radiation in the 290- to 315-nm range emitted. Since skin carcinogenesis is a cumulative response to radiation, it seems important to use light sources with no emission whatever in the 290- to 315-nm range.

Miscellaneous

There still remain several cutaneous photosensitivity diseases that are clearly definable by morphologic criteria but as yet have no known etiology or pathogenesis. These include conditions such as hydroa aestivale, hydroa vacciniforme, and polymorphous light eruption.[18] The latter, polymorphous light eruption, is of importance because of its relatively high incidence in man. The action spectrum is primarily in the 290- to 315-nm range, but cases involving longer wavelengths have been reported. The morphology is exceedingly variable but usually consists of papules on the light-exposed areas occurring 4 to 24 hours following light exposure.

Polyvalent light sensitivity represents another category of photosensitivity disease of unknown pathogenesis but can be an extremely disabling dermatosis. These unfortunate individuals react with erythema and ultimately develop a chronic dermatitis in response to a broad band of wavelengths extending from 290 nm through the visible light range (800 nm). It is suspected that some of these patients may have a specific immunologic reactivity to a drug that elicits the so-called persistent light reaction.[19]

Magnus[20] and his group have described a reaction of similar broad spectrum called actinic reticuloid. They speculate that this may represent another form of persistent light reaction and could possibly be a precursor of a cutaneous lymphoma.

Photoaggravated

The photoaggravated category is used to denote diseases in which the etiology seems to be unrelated to light exposure. Upon exposure to sunlight, however the condition can be worsened or exacerbated. An illustrative example of such a light-aggravated condition would be herpes simplex labialis, a condition known to be due to a virus infection. In this disease, for reasons that are presently not clearly understood, exposure to sunlight in selected individuals harboring this virus causes vesicles to appear on light-exposed areas such as the lip.

The so-called connective tissue diseases may or may not represent an autoimmune process, but there is good agreement that the role of light is not of direct etiologic significance. It has been well established, however, that in selected individuals with systemic lupus erythematosus, exposure to sunlight may lead to enhancement of cutaneous lesions and perhaps a lethal outcome.

Bloom's disease is a childhood disorder of unknown etiology in which skin lesions closely similar to those seen in discoid lupus erythematosus are manifest. In addition, there is retarded growth and development. Exposure to sunlight is associated with marked exacerbation of the skin lesions. This condition is associated with chromosome breaks and may eventuate in a fatal leukemia.

The light-aggravated conditions appear to have action spectra in wavelengths below those usually encountered using conventional phototherapy.

SUMMARY

Solar radiation serves diverse functions in man, the overwhelming majority of which are not only beneficial but essential for life on the earth. Unfortunately, there are selected patients who develop photosensitivity diseases following exposure to specific wavelengths of light. Some of these conditions should be recognized as a potential hazard in phototherapy of the newborn. A working classification of photosensitivity diseases based on etiology is presented to serve as a framework for further investigation in this field.

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Effects of Phototherapy on Hepatic Excretory Function in Man and the Rat [a]

J. Donald Ostrow, Robert G. Knodell, Heidemarie C. Cheney, and Colin S. Berry

Lucey, Ferreiro, and Hewitt [1] presented the first controlled trial of the effects of phototherapy on neonatal jaundice in 1968. Since then, phototherapy has become a widely used procedure in the United States, but much remains unknown about its mechanism of action and its effects on functions other than bilirubin metabolism.

The effects of phototherapy on bilirubin metabolism were first elucidated in our laboratory in 1971 [2] (see figure 1). In this experiment, Gunn

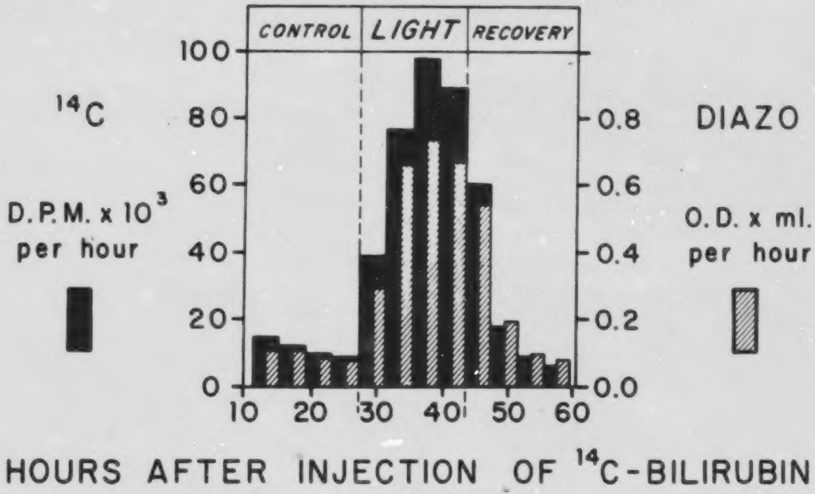

FIGURE 1. Excretion of ^{14}C-radioactivity (solid bars) and of diazo-reactive compounds [3] (cross-hatched bars) in the bile of a 465-gram homozygous jaundiced male Gunn rat before, during, and following phototherapy. The animal was shaved and given 226 micrograms (4.2 microcuries (μc)) of unconjugated ^{14}C-bilirubin at time zero, which was allowed to equilibrate for 11 hours with the endogenous pigment pool. (Reprinted with permission from the *Journal of Clinical Investigation*.[2])

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[a] This research was supported by the Veterans' Administration (6680) and the National Institutes of Health, RO1 AM-14543.

rats with a bile fistula were given a tracer dose of ^{14}C-unconjugated bilirubin intravenously, which was allowed to equilibrate with their pigment pool for a period of 11 hours. Thereafter, collections of bile were made in 4-hour periods, and analyzed for ^{14}C-content and for diazoreactivity by the method of Michaelsson.[3] During a 16-hour control period, the animals were kept under ordinary laboratory illumination of 80 foot-candles. They were then exposed during the light period to 1,600 foot-candles of illumination from General Electric Daylite fluorescent lamps in a special reflecting canopy.[4] Following 16 hours of phototherapy, the lights were again extinguished and a 16-hour recovery period ensued.

During the control period, the output of diazo-reactivity remained relatively constant, whereas the output of radioactivity progressively declined in parallel with the fall of the specific activity of the bilirubin pool. With phototherapy, there was a striking increase in the excretion of both radioactive and diazo-reactive material, which returned to baseline values 8 hours after the lights were turned off. The increase in radioactivity during phototherapy exceeded the increase in diazo-reactivity. This indicated that at least part of the augmented output of labeled material comprised derivatives formed from bilirubin that were less diazo-reactive than the parent pigment.

Additional data indicated that phototherapy altered bilirubin turnover in two ways: (1) There was an accelerated conversion of bilirubin to polar derivatives, which can be excreted in the bile without conjugation. Some of these derivatives have since been identified as dihydroxylated tetrapyrroles.[5,6] (2) There was a remarkable increase in the excretion of unconjugated bilirubin in the bile. This observation has since been confirmed in human neonates[7] and in children with the Crigler-Najjar syndrome,[8] but the mechanism of the increased output of unconjugated bilirubin remains unexplained. One possibility considered was that phototherapy engendered a generalized alteration in the function of the liver, which augmented the excretion of other compounds as well as bilirubin. Such effects, if present, could have therapeutic as well as theoretical implications, since at present there are few methods available[9,10] for stimulating hepatic excretory function in patients with hepatobiliary diseases.

The present paper reports our investigations to date of the following questions: Does phototherapy affect other liver functions? and Is the biliary excretion of other organic anions altered, in particular the excretion of bile salts, bromosulfophthalein (BSP), and conjugated bilirubin?

Our first studies concerned the effects of phototherapy on the excretion of bilirubin and micellar lipids in the bile of Gunn rats. In these experiments, 11 jaundiced Gunn rats were provided with an external biliary fistula under pentobarbital anesthesia. With the animal in a restraining cage, bile was collected in 6- to 10-hour periods on ice and protected from light. Five control rats were kept under dim light throughout the experiment. The other six animals were protected from light for the first 33 hours after biliary cannulation, but then exposed to 1,600 foot-candles from General Electric Daylite fluorescent lamps[4] for the next 18 hours. At the 51st hour after duct cannulation, phototherapy was discontinued and bile collected for another 8 hours. The bile samples were analyzed for diazo-reactivity,[3] bile salts,[11] cholesterol,[12] and phospholipids[13] using standard methods.

Figure 2 shows the effects on excretion of diazo-reactivity, which principally, but not entirely, is due to unconjugated bilirubin.[6] The five control animals exhibited an initial slight drop in the excretion of diazo-reactivity, which slowly and progressively rose thereafter back toward the initial values. By contrast, the six animals exposed to intense light showed a highly significant mean fourfold increase in the output of diazo reactivity while under phototherapy. This rapidly declined toward normal levels when phototherapy was discontinued, indicating that the process was reversible.

Figure 3 shows the excretion of bile salts by the same group of animals. As reported by others,[14,15] with interuption of the enterohepatic circulation, there was a dramatic fall in the output of bile salts in rat bile, which

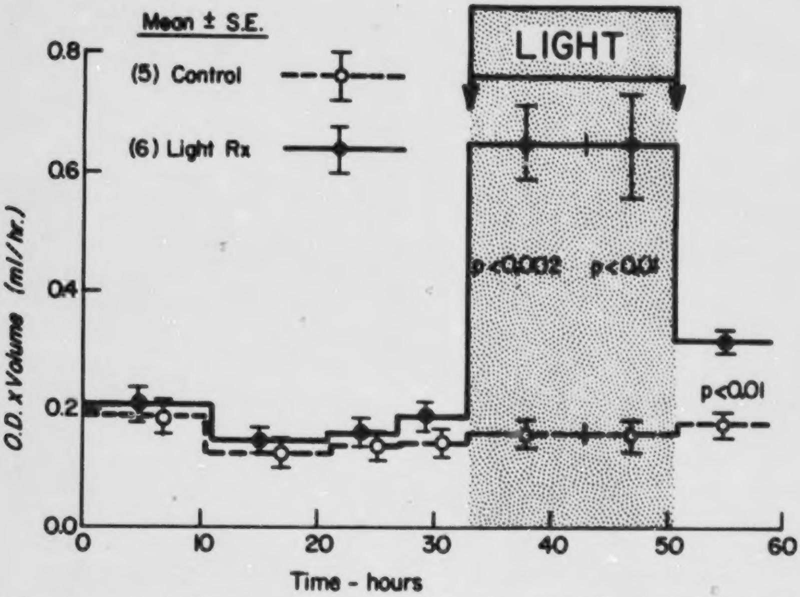

FIGURE 2. Effect of phototherapy on the excretion of diazo-reactive compounds in Gunn rat bile. Total output of diazo reactivity,[3] as optical density multiplied by volume per hour (mean standard error), is shown at different intervals following installation of a bile fistula at time zero. Five control rats were kept under dim light throughout. Six phototherapy rats were exposed to 1,600 foot-candles of illumination (General Electric Daylite fluorescent lamps) during the period from 33–51 hours after bile duct cannulation (stippled zone). (Reprinted with permission from Ostrow, J. D. et al. Effect of phototherapy on bilirubin excretion in man and the rat. *Birth Defects,* 12:81–92, 1976.)

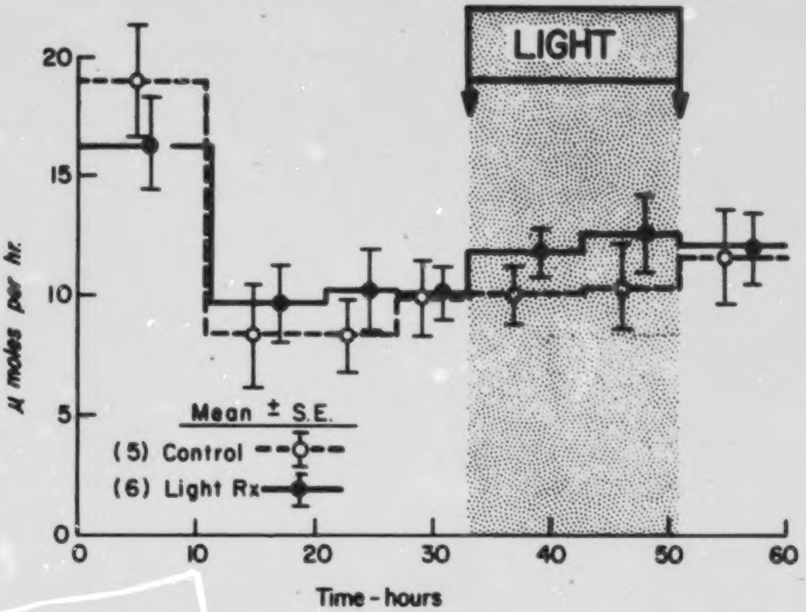

FIGURE 3. Effect of phototherapy on output of bile salts[11] in Gunn rat bile. Animals and presentation of data as in figure 2. (Reprinted with permission from *Phototherapy in the Newborn.*[6])

gradually recovered to a new steady state about 30 hours following duct cannulation. This new plateau of bile salt output was about half that of the initial bile samples. Phototherapy caused no significant increase in the excretion of bile salts in the six animals exposed to intense light. This contrasts strikingly with the effect on bilirubin.

Figure 4 shows the effects on the excretion of cholesterol in these same Gunn rats. In all the animals, the interruption of the enterohepatic circulation led to a marked initial decrease in cholesterol output, which had restabilized at slightly below initial values by the 33d hour.[14,15] As with bile salts, phototherapy had no effect on the output of cholesterol in bile.

Figure 5 illustrates the excretion of phospholipid by these Gunn rats. Again, there is the initial decline and partial recovery in the biliary output of this micellar component.[15] As with the other micellar components, phototherapy did not significantly alter the output of phospholipids in Gunn rat bile. In four other animals, however, not included here, a striking and selective decrease in the output of phospholipids occurred during phototherapy. This was followed by a gradual decline in, and ultimately a virtual cessation of, bile flow. In one of these animals, this cessation was traced to occlusion of the biliary catheter by precipitation of unconjugated bilirubin. In the other three animals, reexploration and liver biopsy revealed no dilatation or obstruction of the bile ducts all the way down to the

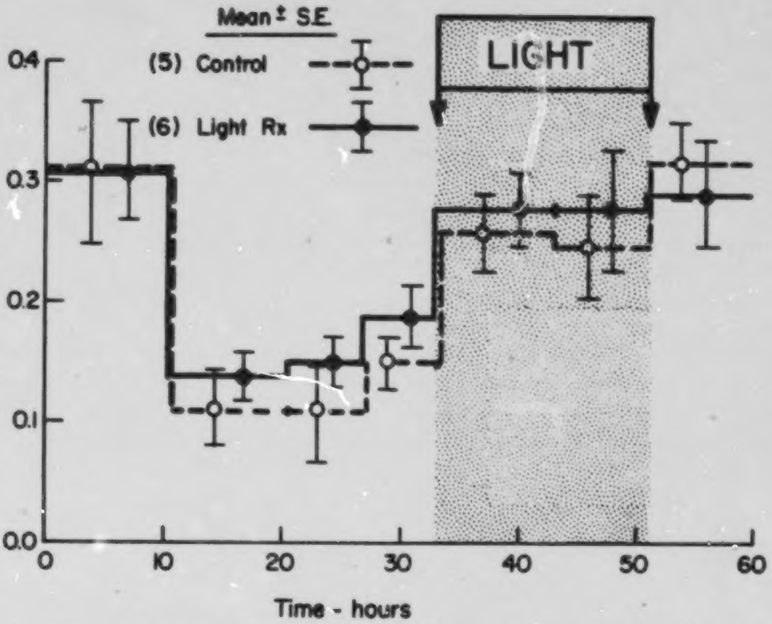

FIGURE 4. Effect of phototherapy on output of cholesterol [13] in Gunn rat bile. Animals and presentation of data as in figure 2.

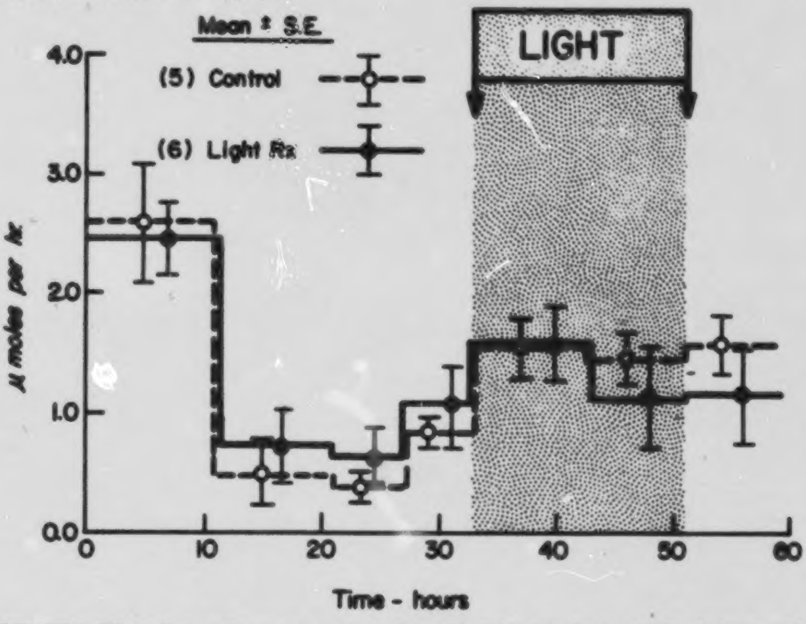

FIGURE 5. Effect of phototherapy on output of phospholipids [13] in Gunn rat bile. Animals and presentation of data as in figure 2.

finest radicles. On histologic examination of the livers (fixation in Bouin's fixative), however, the bile ducts of interlobular size and larger exhibited flattening of the biliary epithelium and periductal accumulation of polymorphonuclear leukocytes. These changes were not observed in the six light treated animals who maintained their bile flow, nor any of four normal rats with biliary cannulae who were similarly treated by phototherapy. To assess the true significance of this worrisome observation, studies need to be performed on the histologic alterations of the liver of Gunn rats exposed to phototherapy without bile duct cannulation.

We next examined the effect of phototherapy on the output of bilirubin in normal rat bile (figure 6). The experiment was conducted identically with those just described in the Gunn rats. Two control rats were kept under light throughout the experiment. The other two animals were exposed to phototherapy during the period from 33 to 51 hours after bile duct cannulation. All four animals behaved similarly, with an initial decline followed by a slow steady increase in the excretion of diazo-reactive pigments in the bile. Phototherapy thus did not alter the excretion of conjugated bilirubin in the bile of normal rats.

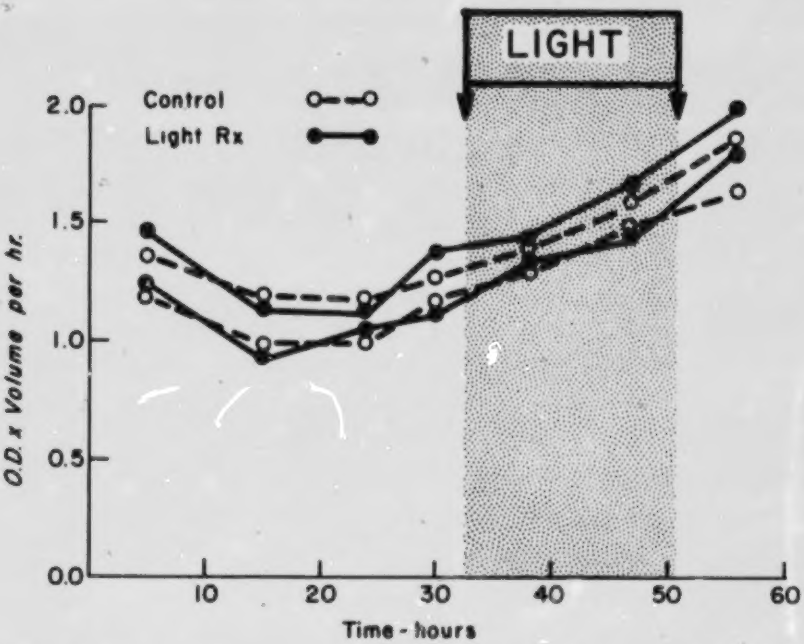

FIGURE 6. Effect of phototherapy on excretion of diazo-reactive compounds[3] in the bile of normal rats. Experiment performed as in figure 2, but with four normal Wistar rats. There were two control rats and two light-treated rats given phototherapy from 33 to 51 hours after bile duct cannulation (stippled zone). (Reprinted with permission from *Birth Defects*, 12:81–92, 1976.)

In interpreting this observation, it must be remembered that phototherapy may exert its major effect on pigment retained in the skin of the animals. Since these normal rats had minimal bilirubin concentrations in the skin, the absence of effect may simply reflect an insufficient amount of pigment exposed to light in the critical cutaneous areas. Therefore, we proceeded to study the effects of phototherapy on the excretion of bilirubin, BSP, and bile acids in six jaundiced patients with stable biopsy-proven alcoholic cirrhosis.

All patients had stable serum liver function tests for at least one week prior to the study. The study was divided into control, phototherapy, and recovery periods of 3 days each. During phototherapy, the patients wore shorts to maximize cutaneous light exposure and remained under General Electric Daylite fluorescent bulbs calculated to deliver 1,000 foot-candles of illumination at the body surface. The eyes were protected by dark glasses. BSP plasma disappearance curves were obtained at the end of each period following a single intravenous injection of 5 milligrams per kilogram. Rate constants for BSP kinetics were determined employing a SAAM digital computer and the kinetic model of Quarfordt et al.[16] Bile acid kinetics were determined by the Lindstedt[17] method, following intravenous administration of tracer doses of ^{14}C-cholic and ^{3}H-chenodeoxycholic acid on the first day. Before breakfast and dinner each day, release of cholecystokinin was stimulated by intraduodenal instillation of an amino acid solution[18] (Freamine, McGaw Laboratories, Glendale, California). The dark B bile that was discharged as the gallbladder contracted was then aspirated via an indwelling nasoduodenal tube. On each sample, bilirubin was determined by the method of Michaelsson;[3] bile acids were enzymatically hydrolyzed with cholylglycine hydrolase[19] and the deconjugated moieties extracted and separated by thin-layer chromatography for determination of specific activity.[20] Because we found that BSP interfered with the determination of bilirubin and bile acids, no analyses of bilirubin or bile acids were performed on samples aspirated during the first 24 hours following each BSP injection.

Figure 7 shows the effect of phototherapy on the serum bilirubin[21] concentration in these cirrhotic subjects. In the six subjects studied, control values ranged from 1.5 to 35.2 milligrams per deciliter total bilirubin, of which 35–60 percent was direct reacting. Three days of phototherapy produced no significant change in the total or direct serum bilirubin levels in these subjects. Nonetheless, in the three white patients who were studied, it was possible to detect a clear-cut decrease in cutaneous icterus on exposed areas of the skin. This suggested that bilirubin turnover had been altered even though serum levels did not change. A similar situation has been previously recorded in some Gunn rats and neonates with unconjugated hyperbilirubinemia.[2,22,23]

This supposition was supported by studies of the effect of phototherapy on the bile bilirubin concentrations[3] (see figure 8). One subject, in whom

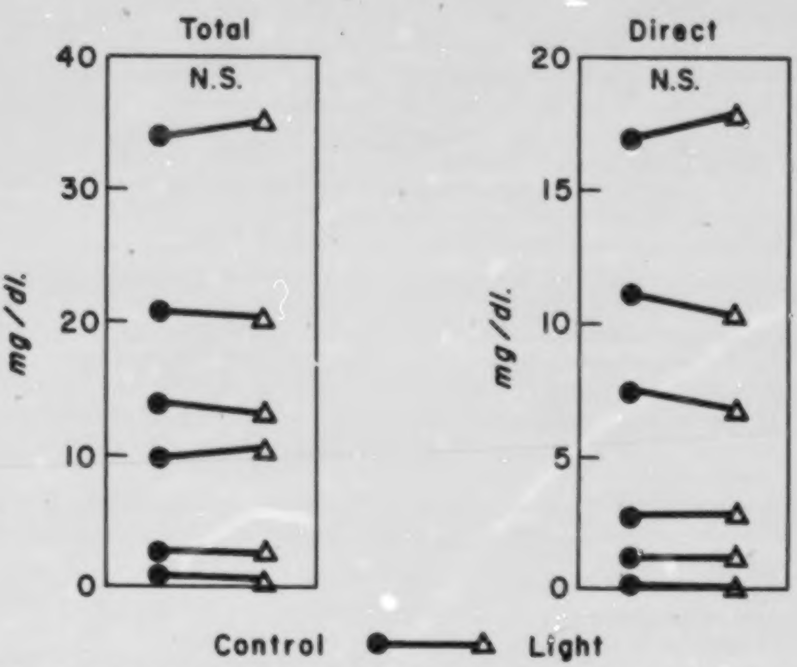

FIGURE 7. Effect of phototherapy on serum total (left) and direct-reacting (right) bilirubin in six patients with stable alcoholic cirrhosis. Serum bilirubin concentrations [illegible] determined during a 3-day control period and after 60 hours of phototherapy. One thousand foot-candles of illumination at body surface was delivered by four General Electric 40-Watt Power-Groove, Daylite fluorescent lamps (Cat.= F489-G17D) mounted in two twin-lamp, 48-inch imperial reflectors (Miller Co., Meriden, Conn., Cat.# IM-2501-04) placed 45 centimeters above the patient. (NS. = not significant.) (Reprinted with permission from *Birth Defects*, 12:81-92, 1976.)

reproducible gallbladder contraction and bile bilirubin concentrations could not be obtained, was omitted. In four of the five subjects for which there was satisfactory data, a clear-cut increase in bilirubin excretion occurred during phototherapy as compared with the control periods. These increased bilirubin concentrations declined toward normal values during the recovery period in the three subjects thus followed. The one subject who did not show an increase in his bile bilirubin had an extremely low concentration of pigment to start with, which may have reflected either impaired gallbladder contraction or extremely poor hepatic excretory function. Thin-layer chromatography of the bile pigments [5,24] and their p-iodoaniline azopigments [25] indicated that as in the Gunn rats,[2,5,6] a minor fraction of the diazo-reactive material excreted during phototherapy represented bilirubin derivatives. Unlike the Gunn rats, however, virtually all the bile bilirubin was in the conjugated form, both during the control and light periods. Bearing in mind that these data represent pigment concentrations measured in duodenal bile after stimulation of gallbladder contrac-

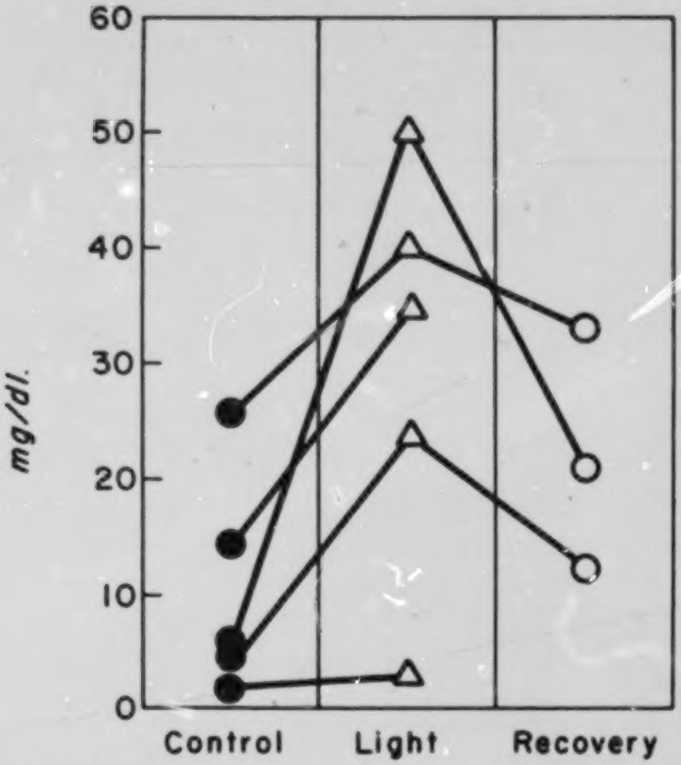

FIGURE 8. Effect of phototherapy on total bile bilirubin concentration [3] in five of the cirrhotic subjects from figure 7. Value for each experimental period represents average of three samples of bile aspirated from the duodenum before breakfast following stimulation of gallbladder emptying by intraduodenal administration of amino acids. (Reprinted with permission from *Birth Defects*, 12:81–92, 1976.)

tion and not bilirubin outputs measured on hepatic bile, the data strongly suggest that phototherapy increases the excretion of conjugated bilirubin in the bile of patients with alcoholic cirrhosis. Additional patients will need to be studied in order to establish whether this is a statistically significant change.

We next wondered whether the improvement in bilirubin excretion reflected a generalized improvement in hepatic function, and whether the excretion of other organic anions was similarly affected. Figure 9 illustrates the effect of phototherapy on serum liver function tests in our cirrhotic subjects. Serum glutamic-oxalacetic transaminase values [26] are shown in the figure. Control values ranged from 25–280 units (normal = less than 20 units) and showed no significant change during phototherapy, although some drop may have occurred in the two patients with the highest values.

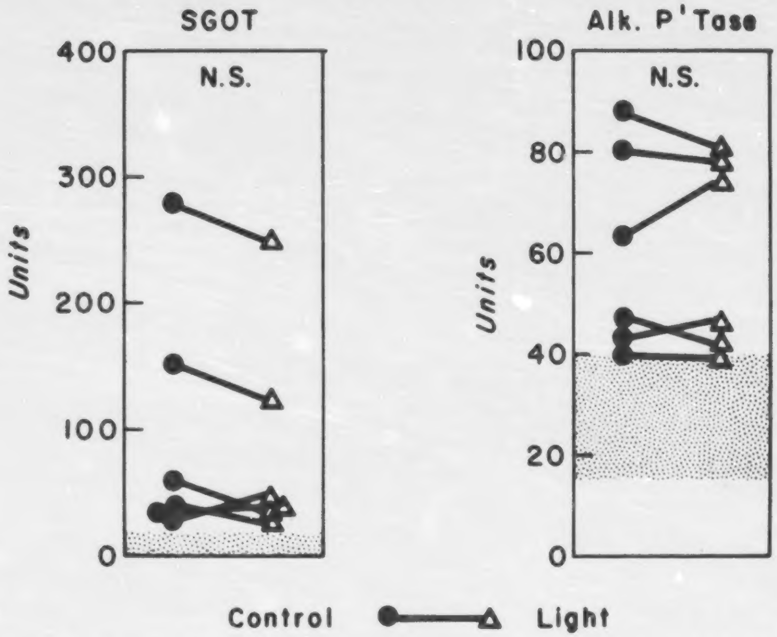

FIGURE 9. Effect of phototherapy on serum liver function tests in the six cirrhotic subjects from figure 7. Serum glutamic-oxalacetic transaminase (left) [26] and alkaline phosphatase (right) [27] values obtained during 3-day control period and after 60 hours of phototherapy. Stippled zones represent normal range of values. N.S. = not significant.)

Serum alkaline phosphatase values,[27] shown in the figure, ranged from 40–88 units (normal = 15–40 units) during the control period. They were likewise not significantly altered by 3 days of phototherapy. Values during the recovery period (not shown) were also unchanged from control, indicating that the patients' intrinsic liver functions were stable throughout the experiment and that the improvement in bilirubin excretion represented a specific and selective effect of phototherapy and not spontaneous remission of their active alcoholic cirrhosis. It also suggests that phototherapy is not harmful to the ailing human liver.

Figure 10 illustrates the plasma disappearance curves for BSP in one patient. All of the other four patients thus examined behaved in identical fashion. The values of serum BSP were followed serially for 2 hours following a single intravenous injection of 5 milligrams per kilogram body weight.[16] It can be seen that the curves before, during, and after phototherapy were virtually superimposable. When these curves were analyzed by computer according to the two compartmental, biexponential method of Quarfordt et al.,[16] no significant changes were found in the fractional transfer rates from plasma into liver (uptake), liver to plasma (reflux), liver to bile (biliary excretion), or plasma to urine (urinary excretion). This

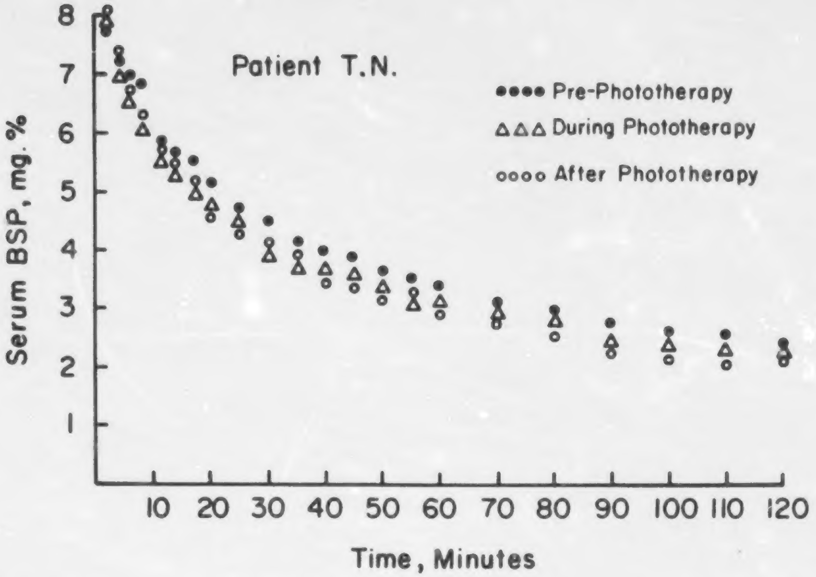

FIGURE 10. Effect of phototherapy on disappearance of sulfobromophthalein (BSP) from serum [16] following a single intravenous injection of 5 milligrams per kilogram. Each study performed on the third day of the respective experimental period. (Reprinted with permission from Knodell, R. G. *et al.*, *Gastroenterology*, 70:1112–1116, 1976.)

indicates that phototherapy did not engender a generalized alteration in hepatic excretory function, and favors a specific effect on bilirubin to account for the increased excretion of bilirubin in the bile. This finding contrasts with the results of Thaler et al.[8] who reported that increased biliary excretion of BSP occurred during phototherapy of a child with the Crigler-Najjar syndrome.

The effect of phototherapy on bile acid turnover is illustrated in figure 11. This shows for one patient the changes in the specific activity of ^{3}H-chenodeoxycholic acid and ^{14}C-cholic acid. The data are plotted semilogarithmically and are representative of the results in all six patients. Initial bile acid pools were cholic acid 116–830 milligrams and chenodeoxycholic acid 186–570 milligrams.[28] In all subjects, there was a semilogarithmic decay in specific activity of both bile acids during the control period. Except for chenodeoxycholic acid in one subject, the slopes of the specific activity decay curves showed striking changes during phototherapy. These included a sudden jump in the specific activity to higher values, followed by an accelerated rate of plasma decay that continued into the recovery period. This evidence of increased bile salt turnover was highly significant for cholic acid ($p<0.02$) but just barely failed to achieve statistical significance for chenodeoxycholic acid ($p<0.10$).

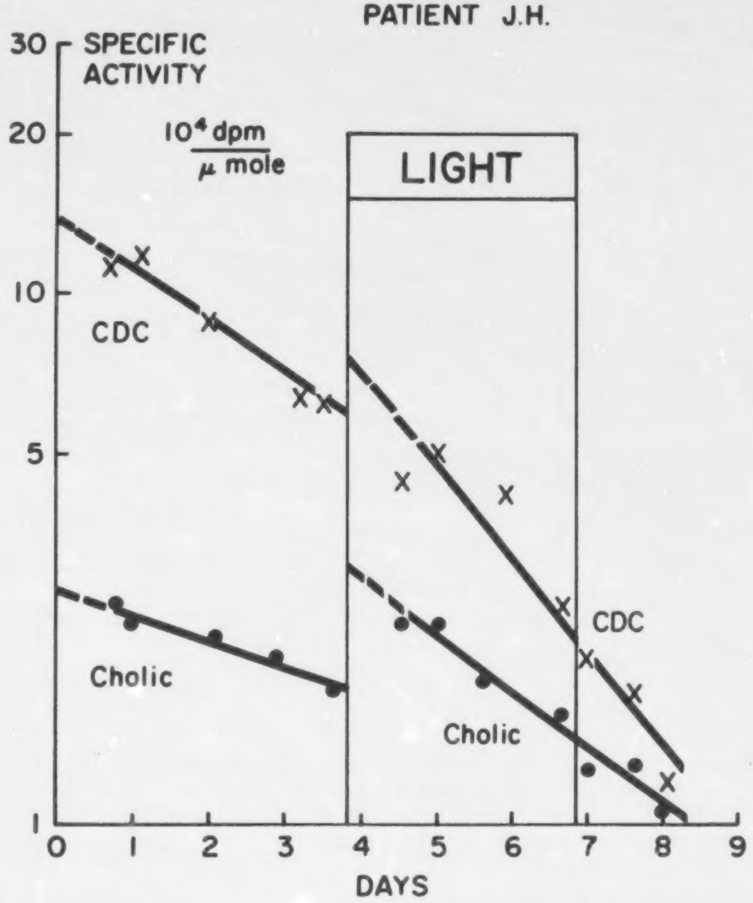

FIGURE 11. Effect of phototherapy on turnover of radio-labeled cholic acid (solid circles) and chenodeoxycholic acid (X's) in a cirrhotic subject. At time zero patient was given 10 μc ^{14}C-cholic acid and 50 μc ^{3}H-chenodeoxycholic acid (CDC) intravenously. Phototherapy was applied during the 72-hour light period. Specific activities were determined on bile acids isolated from specimens of bile aspirated from the duodenum before breakfast and supper, following stimulation of gallbladder emptying by intraduodenal instillation of amino acids. For determination of specific activities, bile was treated with cholylglycine hydrolase,[19] and the unconjugated bile acids were extracted with ether and separated by ascending thin layer chromatography on 5 × 4 centimeter plates of silica gel G, with iso-octane-isopropyl ether-glacial acetic acid (2:1:1 by volume) as the developing solvent.[20] (Reprinted with permission from Knodell, R. G., *et al.* from *Gastroenterology,* 70:1112–1116, 1976.)

The mechanism of this alteration in bile acid turnover is unclear, and whether it resulted in a decrease in serum bile acids has not yet been determined, although the itching of the one subject with pruritis disappeared during phototherapy and returned during the recovery period. This is an interesting observation because of the known, though anecdotal, improvement in the itching of patients with primary biliary cirrhosis during the summertime. The acute jump in bile salt specific activity could result from either mobilization of a highly labeled pool of bile acids or from the conversion of bile acids to labeled derivatives that are not substrates for the hydroxy-steroid dehydrogenase assay. During irradiation of labeled bile acids in vitro in various media, however, we have been unable to demonstrate any alterations either in their chromatographic properties or in their reactivity toward hydroxy-steroid dehydrogenase. The accelerated turnover of bile acids could reflect either an increase in synthesis or an increase in excretion. Preliminary data suggest that the biliary excretion of bile acids was unaltered, but that urinary excretion may be increased. We recognize that the decay curves during phototherapy may represent an unsteady state, and that it may be improper to apply the usual kinetic analysis of first-order decay curves to the phototherapy period.

In summary, the effects of phototherapy on hepatic excretory function in the rat were the following: (1) no change in biliary excretion of bile salts, cholesterol, or phospholipids; (2) augmented excretion of unconjugated bilirubin in Gunn rats but no change in bilirubin excretion in normal nonjaundiced rats; and (3) cessation of bile flow in some Gunn rats. In one rat, the cessation of bile flow was due to precipitation of unconjugated bilirubin in the biliary catheters, but in most there was apparently damage to the biliary epithelium.

The effects of phototherapy on hepatic function in human alcoholic cirrhosis were the following: (1) no change in serum liver function tests, including serum glutamic oxaloacetic transaminase and alkaline phosphatase; (2) no change in BSP excretion or kinetic parameters; (3) increased concentration of conjugated bilirubin of the bile of most patients without a fall in serum bilirubin levels, although a decrease in cutaneous icterus was observed; and (4) increased turnover of cholate and probably of chenodeoxycholate by kinetic studies with labeled bile salts.

The most significant aspect of these studies is the clear demonstration that the turnover of organic anions other than bilirubin may be affected by phototherapy. Phototherapy might therefore have therapeutic value in accelerating the excretion of other compounds, such as drugs, which are normally cleared by the liver. The data also suggest that intrinsic liver function is not altered by phototherapy, and that a direct effect on the organic molecules themselves accounts for the increased turnover of bilirubin and bile salts during phototherapy.

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Discussion

Dr. Schmid: I think Dr. Ostrow has made a very important contribution. If I am correct in interpreting the data, you found an increased turnover of bile acids but no alteration in the metabolism of other organic anions, such as bromosulphalien?

Dr. Ostrow: No change that we could detect.

Dr. Schmid: You also observed that the itching disappeared and you found this very peculiar rise in the specific activity of the bile acids in the bile. The only interpretation that makes sense is that the exogenously administered labeled bile acid did not mix completely with the endogenous pool and that you then mobilized a pool with a high specific activity. That pool may well be in the skin and that is why the itching disappeared. If this is true, then the common assumption of complete mixing would be incorrect; that is, there must be a pool that is rapidly labeled but stays labeled and turns over more slowly than the pool that is increased in the plasma or bile. If this is so, then it would mean that the effect of the light on the skin is directly affecting two compounds that are concentrated in the skin, namely bilirubin and bile acids.

Dr. Ostrow: Actually, I mentioned two possible explanations. One was that the skin pool is more highly labeled than the remaining bile acid pool.

Dr. Schmid: Right. In injecting the labeled bile acids, a certain fraction goes in the skin pool, which then turns over very slowly.

Dr. Ostrow: The point is that we have given the labeled bile acids intravenously to a person with impaired biliary excretion; thus, labeling the enterohepatic pool might be less rapid than the labeling of the skin pool with which the blood is in direct contact.

Dr. Schmid: When you inject the labeled bile acids intravenously, the pool that is present in the plasma is very small, so you are not really injecting a tracer but rather a pharmacological dose.

Dr. Ostrow: These patients have a pool in the plasma that is much larger than normal.

Dr. Schmid: Yes, but it still is relatively small. The plasma pool of bile acids compared to the total body bile acid pool is 1 or 2 percent.

Dr. Ostrow: That is one possibility. The other, of course, is that when we irradiate the bile acids, they are destroyed as far as their chemical reactivity toward steroid dehydrogenase is concerned, thus increasing the apparent specific activity. I do not know which is the correct answer. To answer this question, we are now giving labeled bile acids intraduodenally as well as intravenously to see if we get the same kinetics both ways.

Dr. Schmid: There is one other interesting observation and that is that in alcoholic subjects the increased excretion of bile pigment in bile was conjugated bilirubin, which contradicts the idea that light enhances the ability of the liver to excrete unconjugated pigment.

Dr. Odell: Dr. Ostrow, did I understand you correctly that when patients were under light the urinary excretion of radioactivity or the urinary excretion of bile acids went up?

Dr. Ostrow: We have not analyzed the urine for bile acids. We have only measured the radioactivity and then divided that by the mean plasma specific activity during the corresponding period. There is a four- or fivefold increase.

Dr. Odell: What I would like to suggest is that some of your bile acids get into this very immobile pool in the skin and then with light you release them from the skin and their concentration in the plasma is such that the hepatic uptake is exceeded so that they come out in the urine.

Dr. Ostrow: Yes, that is what we think is reasonable and we are analyzing the urine now to find out.

Dr. Schmid: You have to be careful there because most of the urine bile acids are sulfates. Sulfated bile acids have a high renal clearance. Sulfation can occur in the liver and presumably in the kidney itself so that that may alter your results.

Dr. Miller: May I ask the first speaker about xeroderma pigmentosum. I do not recall whether you said that impaired DNA repair occurs only from ultraviolet exposure, or may it be from the kind of light that is used in phototherapy? Also, in Bloom's syndrome there is photosensitivity. Is that sensitivity also induced by exposure to the light used in phototherapy?

Dr. Bickers: I will answer your second question first. The reason for photosensitivity in Bloom's syndrome is not well understood. I do not think that there are any data to suggest that there is an effect one way or the other. I do not know whether it has been looked for. The wavelengths that appear to be primarily responsible for damage in xeroderma pigmentosum are the wavelengths that elicit skin tumors in man, which is the so-called sunburn spectrum of 290 to 320 nanometers. Thymine dimerization occurs. In a normal situation, these thymine dimers can be excised and a new base sequence inserted. There is evidence that there is a deficiency of the endonuclease that clips out the thymine dimer. Recent studies, however, indicate that in some patients who clinically have unquestionable xeroderma pigmentosum, DNA repair is normal by in-vitro testing. There may be various forms of what we clinically call xeroderma pigmentosum.

Dr. Schmid: Is it not true that we have five or six different repair systems?

Dr. Bickers: Yes.

Dr. Schmid: So a genetic defect may affect only one of these.

Dr. Bickers: That is correct.

Dr. Miller: The wavelengths of phototherapy then are of no particular concern in these diseases, but one speaker did show an increased number of wheals on exposure to wavelengths used in phototherapy as well as below that.

Dr. Bickers: In erythropoietic protoporphyria, yes.

Dr. Miller: That is the only circumstance under which the phototherapy wavelengths have been observed to produce some form of skin sensitivity?

Dr. Bickers: In children.

Dr. Brown: Excuse me. What do you mean by phototherapy wavelength? Do you mean the presumed effective wavelength for phototherapy or that actually used?

Dr. Miller: I mean actually delivered.

Dr. Brown: There is no delivery in these wavelengths?

Dr. Bickers: There is almost none of the sunburn spectrum. I have something from GE here on these questions. I could pass it around if you want to take a look at it.

Dr. Schmid: All right.

Dr. Vogl: The problem with the graphs that the light bulb companies put out is that they are on a linear scale. There was a recent paper that pointed out that for many of these lamps, if careful measurements of light output are made, there is appreciable light output in the shorter wavelength bands. By their calculations, the amount of radiation in the actinic band delivered through 3 days of phototherapy is several times the minimal erythemal dose.

Dr. Bickers: But is there erythema?

Dr. Lois Johnson: Is there still significant emission in those wavelengths through a Plexiglas shield?

Dr. Vogl: The answer to that question is that there is not just one kind of Plexiglas. One can get Plexiglas with properly incorporated ultraviolet absorbers that will transmit essentially no radiation in that region, but to simply say Plexiglas is not enough to answer this question.

Dr. Hastings: You did not mention the clinical use of beta carotene to treat some of these diseases. Are some of them, indeed, relieved by dietary beta carotene? Have all of them been checked with regard to that? Can one distinguish them clinically by the effect of beta carotene?

Dr. Bickers: Beta carotene is still an experimental drug for use in erythropoietic protoporpyria (EPP). Dr. Harber's group is one of several that are experimenting and using this drug in EPP. There is no question that there is significant subjective benefit to patients with this disease in terms of their photosensitivity. There is absolutely no effect on their protoporphyrin excretion, red cell protoporphyrin level, etc. It has no effect on the protoporphyrin excess. It does appear to have a photoprotective effect in this disorder. We have used it in porphyria cutanea tarda in a very limited number of patients without any definite benefit. The use in other photosensitivity diseases to my knowledge, has not been adequately studied to give a definitive answer.

Dr. Hastings: You are saying that the answer is yes. There is a difference between diseases with respect to the efficacy of beta carotene?

Dr. Bickers: Absolutely.

Dr. Hastings: In some it works, in some it does not.

Dr. Bickers: That is correct.

Dr. Hastings: You can then perhaps distinguish between those diseases that involve a photosensitizing agent and those in which the action of the light is directly on the target molecule being affected. Would you conclude that?

Dr. Bickers: Not necessarily. The reason why beta carotene is effective in EPP is not completely understood. It does absorb strongly in the 400- to 500-nanometer range.

Dr. Hastings: It is believed to quench excited singlet oxygen.

Dr. Bickers: That is correct.

Dr. Hastings: I think the evidence for that is very good.

Dr. Bickers: Yes, there is strong evidence for beta carotene acting as a free radical quencher in certain systems, and also as a singlet excited oxygen quencher in some other systems. The mode of action in vivo in EPP, however, has not been clearly defined at this time.

Dr. Hastings: Would you say so, Dr. McDonagh?

Dr. McDonagh: Yes, but it is not known to what extent it is acting as a shield or as a quencher. In vitro, it is certainly a very powerful quencher, and probably this is true in plant leaves, as you mentioned earlier, and in patients. A recent study by Swanbeck and Wennersten (*Acta Dermatovener,* 53:283–289, 1973) showed that the inhibitory effect of beta carotene on photosensitized hemolysis of red cells in vitro is due entirely to quenching and not to a shielding effect caused by absorption of light by beta carotene.

Dr. Indyk: The recent concern over supposed erythema of two babies in Montana was based on measurements that were also reported at the recent Optical Society meeting. The number of photons in the ultraviolet spectrum was approximately 1,000 to 10,000 below the number of photons in the visible spectrum; therefore, it does not appear on the linear graph, but there is some emission down at 290 nanometers. I think 292 and 302 or 303 nanometers were the wavelengths reported. If you buy Plexiglas-G, which is in common use and is the cheapest, you do get very effective blocking of radiation down around 300 nanometers. You have to pay considerably more when you order Plexiglas that transmits this band of ultraviolet.

Dr. Kapitulnik: Dr. Ostrow, I think your presentation raises very new and interesting questions. One of the findings of interest to me was that you did not observe a change in the excretion of unconjugated bilirubin in the normal nonjaundiced rats. In normal rats there was no increase or change in the excretion of nonconjugated bilirubin?

Dr. Ostrow: In normal rats there is virtually no unconjugated bilirubin in the bile, but there actually is a slight increase in the output of unconjugated bilirubin during phototherapy. It is insignificant, however, in terms of the total change in bilirubin excretion.

Dr. Kapitulnik: Since in the jaundiced rat it was shown that there was an increase in the concentration of unconjugated bilirubin in the bile in phototherapy, what do you think would be the case if you injected bilirubin into a normal rat and then measured the effect of phototherapy?

Dr. Ostrow: This is a very good suggestion, but a difficult experiment because bilirubin injected intravenously into a normal rat shoots out into the bile very rapidly. Therefore, you have to use a constant infusion technique. I think the experiment is worth doing to answer this particular question.

Photochemistry and Photometabolism of Bilirubin [a]

Antony F. McDonagh

The macroscopic effects of phototherapy on jaundiced infants (blanching of the skin and lowering of the serum bilirubin concentration) are well known [1,2] but not much is known about the molecular events that cause these effects. Consequently, the mechanism of phototherapy is obscure. Obviously the first step in the process must be absorption of light by some compound(s) within the exposed tissue, since light has to be absorbed to produce a photobiological response. Although the action spectrum for phototherapy has not been determined, light of wavelengths between 440 and 470 nanometers (nm) is evidently the most effective in reducing serum levels of bilirubin, and wavelengths outside this region have little effect.[3] Since this wave band corresponds to the absorption band of bilirubin in chloroform or serum and since bilirubin is the most obvious chromophore in the skin, subcutaneous tissue, and serum of jaundiced infants, it may be assumed that the photobiologically active absorbing compound in phototherapy is bilirubin (B). If this is correct, the initial event in the mechanism of phototherapy must be formation of an excited bilirubin molecule (B^*) by absorption of a photon (equation 1), and the further sequence of events leading to the macroscopic effects of the treatment will depend on the subsequent thermal or dark reactions of this transient metastable excited-state molecule.

$$B + h\nu \rightarrow B^* \qquad (1)$$

Optical excitation of bilirubin in vivo or in vitro could generate two types of excited-state species. A short-lived singlet-state molecule would be formed initially having all electrons paired. But this could change, by a process called intersystem crossing, to a longer-lived triplet-state molecule containing an uncoupled pair of electrons. Either of these excited-state bilirubin molecules might have chemical and biological properties quite different from ordinary ground-state bilirubin. For example, triplet-state bilirubin, with its unpaired electrons, would be expected to behave as a free radical.

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[a] This work was aided by grants from the Duro-Test Corporation, North Bergen, N.J., and by the United Cerebral Palsy Research and Education Foundation.

Excited-state bilirubin could undergo three general processes. It could revert to the ground-state and release its photochemically derived energy as thermal energy (E) (equation 2).

$$B^* \rightarrow B + E_{\text{thermal}} \tag{2}$$

Although this is usually a trivial process in photochemical reactions, it may not be trivial in vivo at the cellular level since the energy involved is likely to be of the order of 50 kilocalories per mole. Second, the excited molecule (B^*) could transfer its excitation energy to some other molecule (X) to give ground-state bilirubin (B) and a different excited-state substance (X^*) (equation 3).

$$B^* + X \rightarrow B + X^* \tag{3}$$

This newly formed excited-state species could then undergo further chemical reactions, or decay back to its ground state with thermal loss of its excitation energy. In vivo, where bilirubin is largely associated with protein, the receptor molecules would be restricted to binding proteins or freely diffusible unsaturated substances such as oxygen, since the energy-transfer process requires collision between bilirubin and the receptor molecule. Third, photochemically excited bilirubin could undergo chemical reaction either by itself (equation 4) or by interaction with other metabolites (Y) (equation 5) to give products.

$$B^* \rightarrow \text{Products} \tag{4}$$

$$B^* + Y \rightarrow \text{Products} \tag{5}$$

All of the preceding processes could occur in vivo during phototherapy, but at present it is not known which of them occurs to a physiologically significant extent or which is responsible for the phototherapeutic effects of the treatment. Some insight into the probable reactions of excited-state bilirubin in vivo can be obtained from studies of bilirubin photochemistry in vitro. It must be recognized, of course, that the static homogeneous solutions generally studied in vitro may not be adequate models for the dynamic heterogeneous conditions in the jaundiced child. Nevertheless, a comprehensive knowledge of bilirubin photochemistry will undoubtedly help to elucidate the mechanism of phototherapy and identify potential hazards of the treatment. In the remainder of this paper, I shall review the known photochemical reactions of bilirubin and consider which of these are likely to occur during phototherapy and contribute to the photometabolism of bilirubin in the jaundiced infant.

PHOTOCHEMICAL REACTIONS OF BILIRUBIN

The photochemistry of bilirubin, like that of many other highly unsaturated compounds, is complex. The pigment undergoes different reactions depending on the nature of the solvent, the wavelength of the activating light, the concentration of oxygen, and the nature of other compounds present in the solution. These reactions may be divided into two groups depending on whether they require molecular oxygen, and these groups may be subdivided according to the mechanism of the reaction or the nature of the products. On this basis, six reactions may be distinguished.

Photoisomerization

When deoxygenated solutions of bilirubin IX-α in aqueous buffer (pH 7.4–8.5) are irradiated with visible light, the pigment is slowly converted to a mixture containing bilirubin III-, IX-, and XIII-α (figure 1).[5] In addition,

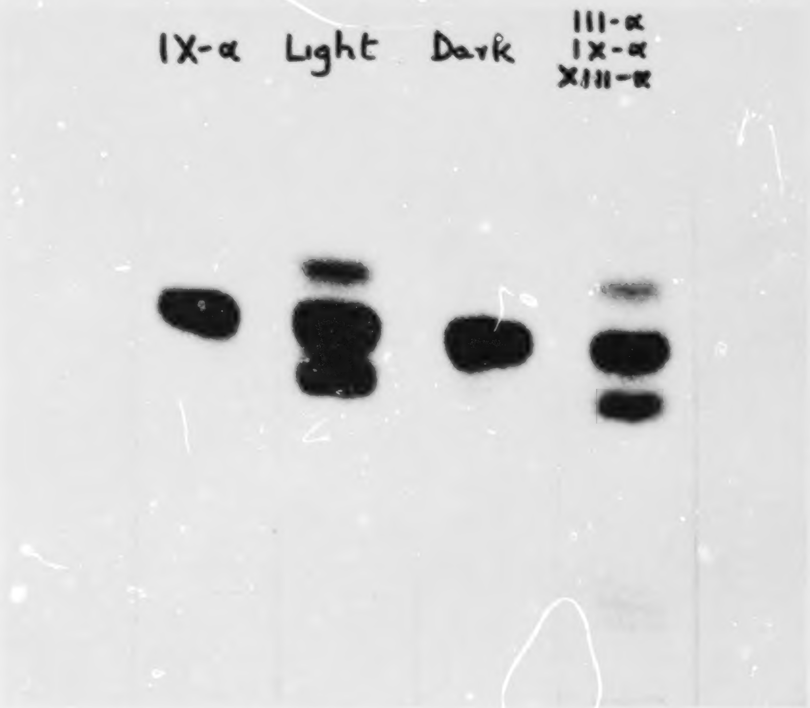


FIGURE 1. Thin-layer chromatography of pigments obtained by photoisomerization of bilirubin IX-α. (Bilirubin IX-α [2.5 milligrams] in 0.05 M [molar] tris buffer [pH 8.5; 100 milliliters] was irradiated for 6 hours under argon through plate glass with a 400-watt high pressure mercury lamp. Bilirubin was recovered by chloroform extraction and analyzed by thin layer chromatography on silica gel.[4] *Left to right*: Starting material; product; product from unirradiated control; mixture containing authentic samples of the three bilirubin isomers.)

the pigment gradually decomposes to uncharacterized materials. This reaction, which has the overall equation shown in figure 2, is the photochemical

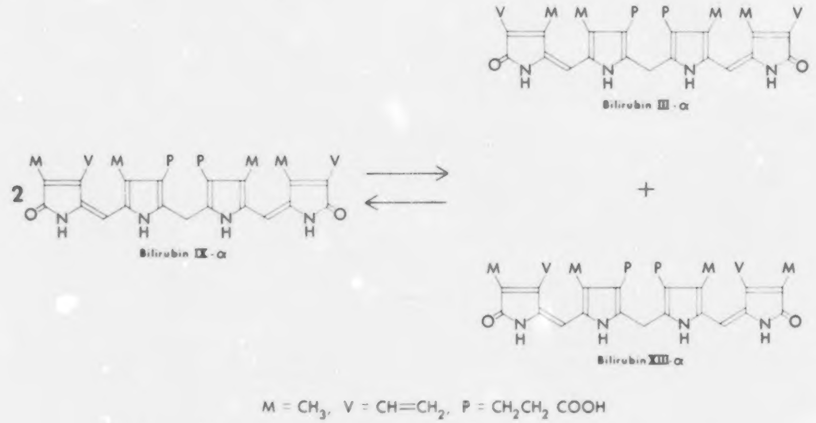


FIGURE 2. Isomerization of bilirubin IX-α to bilirubin III-and XIII-α.

analogue of the isomerization reaction of bilirubin IX-α, which occurs in aqueous buffer at similar pH values in the dark in the presence of oxygen.[6] The mechanism of the reaction has not been established, but it appears to be a free radical chain process and the following mechanism has been proposed ($A\text{-}CH_2\text{-}B$ = Bilirubin IX-α).[5]

Initiation:

$$R\cdot + A\text{-}CH_2\text{-}B \rightarrow AR + \cdot CH_2\text{-}B$$
$$R\cdot + A\text{-}CH_2\text{-}B \rightarrow A\text{-}CH_2\cdot + RB$$

Propagation:

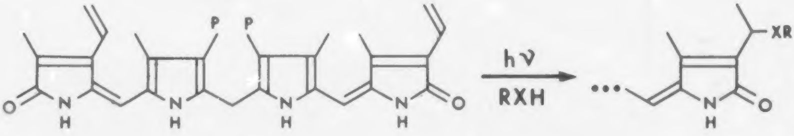
$$A\text{-}CH_2\text{-}B + \cdot CH_2\text{-}B \rightleftarrows B\text{-}CH_2\text{-}B + A\text{-}CH_2\cdot$$
$$A\text{-}CH_2\text{-}B + \cdot CH_2\text{-}A \rightleftarrows A\text{-}CH_2\text{-}A + B\text{-}CH_2\cdot$$

In the initiation step, an unidentified photochemically-generated free radical attacks bilirubin IX-α causing cleavage of the molecule at either side of the central bridge. This leads to the formation of two isomeric resonance-stabilized dipyrrylmethene free radicals that can then attack bilirubin leading to formation of the symmetrical isomers and further radicals.

The photoisomerization reaction appears to be specific to mildly alkaline solutions of bilirubin in hydroxylic solvents, and even under these conditions it is not observed if oxygen is present, owing to the more rapid photo-oxidation of the pigment. Irradiation of solutions of bilirubin in 0.1 *N* NaOH, chloroform, dimethyl sulfoxide, or aqueous bovine serum albumin (pH 8.5) does not result in significant photoisomerization.[5] Therefore, the reaction is unlikely to occur in vivo during phototherapy. In agreement with this, it has been found that prolonged irradiation of depilated homozygous Gunn rats does not lead to the accumulation of bilirubin III- and XIII-α in the serum, even when the common bile duct is ligated before the irradiation to curtail elimination of photoproducts.

Photoaddition

When bilirubin is irradiated in the presence of alcohols or thiols, addition of the alcohol or thiol across the *exo*-vinyl group of the tetrapyrrole may occur (figure 3).[7–9] Compounds that have been shown to add in this way include primary and secondary alcohols, 2-mercaptoethanol, glutathione, and N-acetyl-l-cysteine. The Markovnikoff stereochemistry of the addition indicates an ionic mechanism for this reaction and suggests that it is excited singlet-state bilirubin that is involved rather than triplet bilirubin, since the latter would be expected to undergo a free-radical type of addition. It has been postulated that photoaddition of nucleophiles to bilirubin may be an important factor in the mechanism of phototherapy since this could lead to formation of more water-soluble and more readily excretable tetrapyrroles.[10] This hypothesis cannot be tested until the structures of the photoproducts, which are formed in vivo, have been determined. In general, however, the photoaddition reaction is slow and yields of the photoproducts are low unless oxygen is excluded from the medium. On this basis, it seems unlikely that photoaddition would be an important process in vivo.



Bilirubin IX-α

X= O,S

FIGURE 3. Photoaddition of alcohols and thiols to bilirubin IX-α.

Conversion to Unidentified 443-nanometer Pigment

A yellow pigment with a single visible absorption maximum at 442–444 nm in chloroform or at 433 nm in water at pH 8.5 is formed slowly when solutions of bilirubin IX-α in buffer (pH 7.4 or 8.5), aqueous albumin, or rat serum are irradiated with visible light.[11] Yields of this pigment are generally low, but they are highest when albumin is present and oxygen is excluded from the solution. Under optimal conditions, the yield is about 13 percent (assuming that the compound has a molecular weight of 600 and a molar extinction coefficient of 60,000). The remainder of the product consists of unreacted starting material (20–30 percent) and several other uncharacterized compounds. Like bilirubin, the pigment is soluble in chloroform and can be chromatographed on thin polyamide layers. Unlike the natural pigment, however, it is unstable on silica gel layers, is readily extractable from chloroform solutions into 0.1 M aqueous $NaHCO_3$, and fails to give positive diazo and pentdyopent reactions. On electron impact or chemical ionization mass spectrometry, the compound failed to give a distinct parent or molecular ion and only weak fragments of low molecular weight could be detected. Following treatment with *p*-toluene sulfonic acid in chloroform, the compound was largely recovered unchanged, indicating the absence of hydroxylated vinyl side chains. At present, the structure of this pigment is unknown. When homozygous Gunn rats were exposed to strong visible light for prolonged periods, the pigment could not be detected in the serum, even when the common bile duct was ligated prior to irradiation. It seems unlikely that this obscure bilirubin degradation product is of any importance in phototherapy.

Formation of Unidentified 430-Nanometer Compound

Irradiation of solutions of bilirubin in aqueous albumin results in formation of unspecified yields of a yellow ultrafiltrable pigment with λ_{max} = 430-435 nm in 0.1 M veronal buffer, pH 8.4, as well as several other uncharacterized products.[12] This pigment, which is soluble in chloroform and does not give a typical diazo or positive pentdyopent reaction, has not been completely characterized or identified. Its properties are suggestive of a dipyrrylmethene and resemble those of the pigment described in the preceding section, to which it may be identical. Interest in this pigment has been stimulated by the detection of a similar compound in the serum and excreta of an infant with Crigler-Najjar syndrome undergoing phototherapy.[12, 13] The same material was also detected when the patient was not receiving phototherapy.[13] At present, it is an open question whether "430 pigment" is a major or important photoproduct of bilirubin in vivo during phototherapy.

Photooxygenation

When solutions of bilirubin are irradiated with visible light in the presence of air or oxygen, the pigment decomposes rather rapidly. This is a well-known process that has been extensively studied because of its probable occurrence during phototherapy. The kinetics, mechanism, and end products of the photodecomposition vary with the experimental conditions, especially the nature of the solvent and the initial concentration of bilirubin. In homogeneous solutions, the pigment appears to be degraded by two main pathways that may involve a common intermediate in the initial stages. One pathway leads to oxygenated derivatives of bilirubin and lower molecular-weight breakdown products; the other, which is discussed separately below, is overall a dehydrogenation reaction and leads to biliverdin.

Irradiation of bilirubin in ammoniacal methanol yields methylvinylmaleimide, hematinic acid imide (figure 4), and three of the four possible isomeric methanol-propentdyopent adducts shown in figure 5 as major products.[14–20] In addition, variable amounts of biliverdin [15, 17, 21] and small amounts of water-propentdyopent (figure 5) [16] and polymeric material [20] are also formed. With water as the solvent, similar products are obtained except that water-propentdyopent adducts (figure 5) are formed rather than the corresponding methanol adducts.[17, 19] The dipyrrylmethane dialdehyde shown in figure 4 has also been isolated as a minor product from the photooxygenation of bilirubin in water.[16]

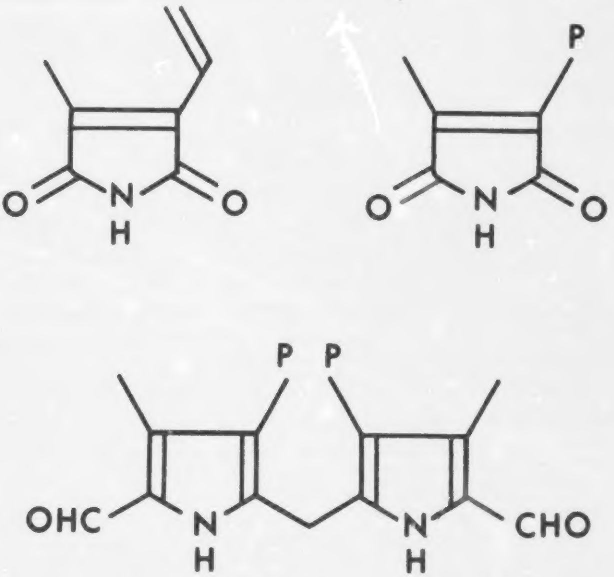


FIGURE 4. Photooxygenation products of bilirubin IX-α *Top:* Methylvinylmaleimide, hematinic acid imide. *Bottom:* 3,3′-di (2-Carboxyethyl)-5,5′-deformyl 4,4′-dimethyl dipyrrylmethane.

The photodecomposition of bilirubin in serum or aqueous albumin has been studied by several groups, but the photoproducts have not yet been definitively identified. It has been reported that irradiation of bilirubin-albumin solutions in air leads to formation of the dipyrrylmethane dial-

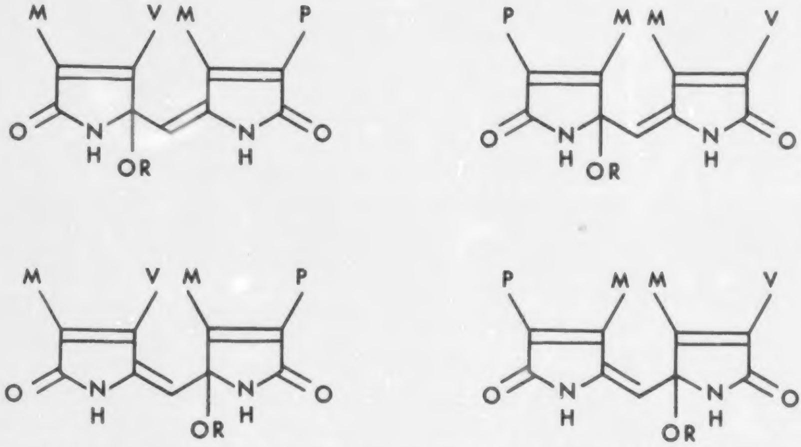


FIGURE 5. Photooxygenation products of bilirubin IX-α. Isomeric methanol (*R* = CH_3) or water (*R* = *H*) propentdyopent adducts.

dehyde shown in figure 4 and several tetrapyrrole pigments analogous to biliverdin and bilirubin, but with hydroxyl or carbonyl functions at the bridge positions.[1] Although binding of bilirubin to albumin might be expected to influence the mechanism of the reaction,[22] it would be surprising if maleimides and water-propentdyopents were not also formed to an appreciable extent as in protein-free aqueous solutions.

In chloroform solution, biliverdin formation may be substantial and greater than in hydroxylic solvents.[15, 21] The yields of biliverdin are markedly concentration dependent, however, and tend to decrease with decreasing initial concentration of bilirubin.[21] The amount of biliverdin formed and the nature of the other products may also depend on whether the chloroform solvent is pure or contains the usual 1–2 percent ethanol stabilizer. In addition to biliverdin, several products, including propentdyopents, maleimides, and open-chain carboxylic acids, are formed on exposure of solutions of bilirubin in chloroform to diffuse daylight for prolonged periods.[23] On the other hand, short-term irradiation of solutions of bilirubin in pure chloroform yields a number of products that include three novel tetrapyrrolic pigments of the rubin, rhodin, and purpurin type (figure 6).[24] The yields of these pigments were not reported and their structures have not been unambiguously established. Their importance rests on the finding that identical compounds occur, inter alia, in normal Gunn rat bile with increased amounts present during phototherapy.[24]

Although the photooxygenation of bilirubin leads to several products, their formation is readily accounted for by a unifying mechanism involving singlet oxygen (i.e., molecular oxygen in its first excited singlet state). Bilirubin is a weak photosensitizer. On irradiation in solution in the pres-

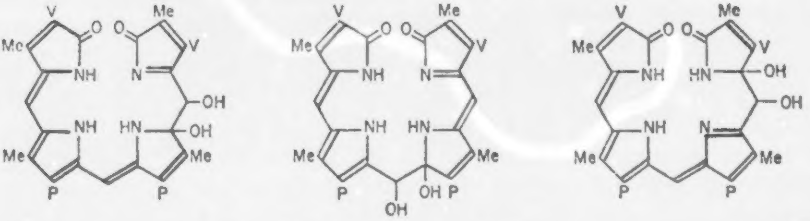


FIGURE 6. Proposed structures of three of the products formed on photooxygenation of bilirubin in chloroform.

ence of air, the pigment sensitizes singlet oxygen formation by transfer of excitation energy from its first excited triplet state to ground state molecular oxygen (cf. equation 3; $X = O_2$).[19, 25, 26] In addition, bilirubin reacts very rapidly with singlet oxygen.[25,27] Hence, irradiation of bilirubin produces singlet oxygen that can attack the pigment to give photodegradation products. The dominant modes of attack of singlet oxygen on bilirubin appear to be 1,2-addition at the enamine-like *a* and *c* bridges to give a dioxetane, and 1,4-addition to either of the central pair of pyrrole rings to form a cyclic endo-peroxide (figure 7). The resulting oxygenated tetrapyrroles,

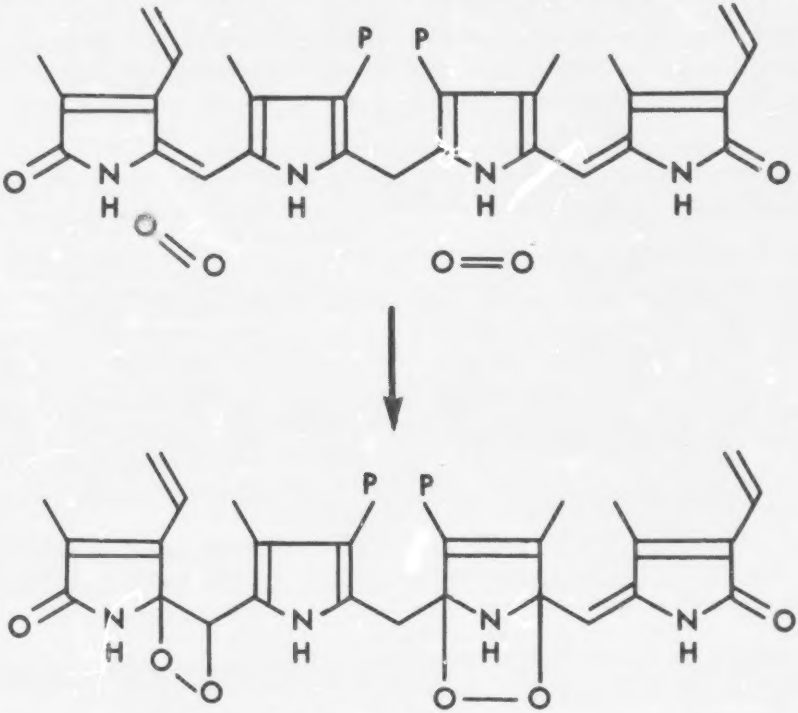


FIGURE 7. The two main modes of attack of singlet oxygen on bilirubin.

which have not been isolated, can react further to give products. Rearrangement of a dioxetane type of intermediate would yield methlvinylmaleimide and a tripyrrolic aldehyde that could react further with singlet oxygen in a similar fashion to give another molecule of the imide and the dipyrrylmethane dialdehyde shown in figure 4.[25] The latter, by analogy with other pyrrole aldehydes, would also react readily with singlet oxygen to give hematinic acid imide (figure 4).[17] Rearrangement of an endoperoxide type of intermediate, either internally or by interaction with solvent (ROH), would be expected to give hematinic acid imide or propentdyopent adducts as observed.[14, 15, 17] It has been suggested recently, on the basis of kinetic data, that freely diffusing singlet oxygen is not present during the photooxygenation of bilirubin in solution.[27] This suggestion is hard to reconcile with earlier studies of the reaction. There is considerable evidence to support the self-sensitized singlet oxygen mechanism as the major pathway for the photodegradation of bilirubin in most of the systems studied and the isolation of maleimides and propentdyopents as major photooxygenation products is in good agreement with this mechanism.

Although bilirubin is a poor photosensitizer for singlet oxygen, it is very reactive toward it. This has been amply demonstrated by studies in which singlet oxygen was generated physically (using direct laser irradiation of molecular oxygen),[27] chemically (using triphenylphosphite ozonide),[28] or photochemically (using sensitizers such as rose bengal, methylene blue, octaethylporphyrin, or riboflavin).[25, 26, 29] The high reactivity of bilirubin toward singlet oxygen explains why its rate of photodegradation is enormously enhanced by the presence of small amounts of efficient singlet oxygen photosensitizing dyes in the solution.[25, 26, 29] Furthermore, the weak photosensitizing properties of the pigment coupled with its high avidity for singlet oxygen may explain why it does not cause patent photodynamic damage in the jaundiced infant.

The relative ease with which biliverdin undergoes photooxygenation under a variety of conditions in vitro emphasizes the high probability of this reaction occurring in vivo during phototherapy.

Photooxidation to Biliverdin

As mentioned above, photooxygenation of bilirubin is generally accompanied by dehydrogenation of the pigment to biliverdin (figure 8), and under certain conditions this may be the predominant reaction. For example, biliverdin is formed in almost quantitative yield when bilirubin is irradiated in benzene in the presence of oxygen.[28] Oxygen may not be required for the conversion, however, since prolonged irradiation of bilirubin under nitrogen also gives a quantitative yield of a verdinoid pigment, thought to be biliverdin.[30] In general, biliverdin formation appears to be favored by nonpolar or aprotic solvents and high initial bilirubin concentrations.[15,21]

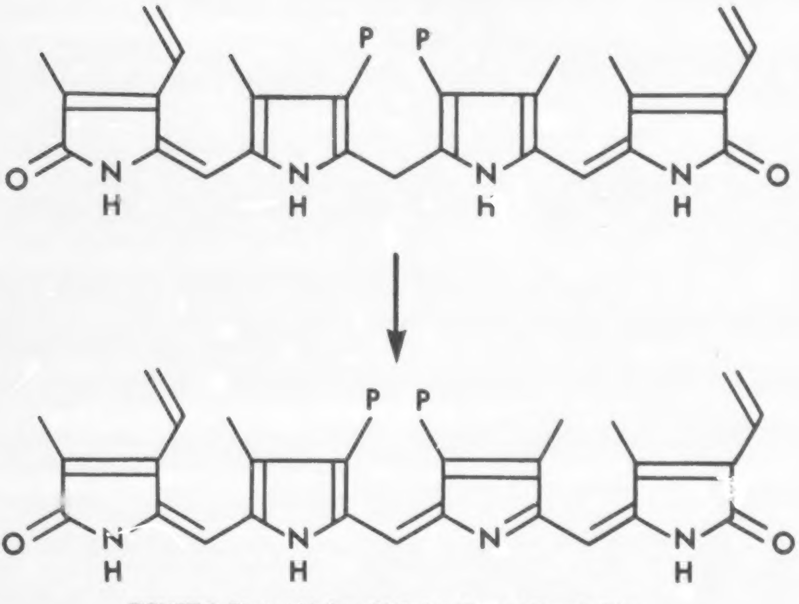


FIGURE 8. Photooxidation of bilirubin XI-α to biliverdin IX-α.

The mechanism of biliverdin formation is not clear. The reaction may be a free radical process in which the first step is loss of a hydrogen atom from the central methylene bridge of the bilirubin molecule giving a reactive resonance-stabilized bilirubin free radical. Alternatively, the reaction could proceed by addition of singlet oxygen to one of the central pyrrole rings to give an endo-peroxide, as in the photooxygenation reaction (cf. figure 7). In the absence of nucleophilic solvent molecules, the endo-peroxide intermediate could then eliminate hydrogen peroxide to give biliverdin.

Biliverdin was originally considered to be the primary product of bilirubin photooxidation and the precursor of all the other bilirubin photoproducts.[31] but this view has been shown to be incorrect.[21, 32] Although biliverdin, like bilirubin, can be photooxidized to maleimides and propentdyopents,[17,33] the reaction occurs at a considerably slower rate than the corresponding photodegradation of bilirubin. Compared to bilirubin, biliverdin is quite stable to photooxygenation.[32]

It is difficult to predict whether photooxidation of bilirubin to biliverdin might occur in vivo. The slow rate of the reaction and the protic milieu of the body make it seem unlikely. Even if it does occur during phototherapy, however, it would probably be inconsequential since any biliverdin formed would be reduced back to bilirubin by biliverdin reductase.[34]

PHOTOMETABOLISM OF BILIRUBIN

Studies on jaundiced infants, patients with the Crigler-Najjar syndrome, and homozygous jaundiced Gunn rats have demonstrated that phototherapy has two readily observable effect on bilirubin in vivo.[1,2] The yellow color of the skin exposed to the light becomes bleached, and this is generally accompanied by a drop in the concentration of bilirubin in the blood, indicating destruction or elimination of the pigment. In addition, phototherapy may cause other physiological effects, such as increased peripheral blood flow,[35,36] augmented gut transit time,[37] enhanced insensible water loss,[35,38] and the appearance of loose green stools.[37,39] It is by no means certain, however, that all of these "secondary" effects are dependent on the interaction of light with bilirubin in exposed tissues.

By means of isotope studies, in which Gunn rats and Crigler-Najjar patients were labeled with radioactive ^{14}C-bilirubin, it has been shown that phototherapy stimulates a large increase in the excretion of the isotopic label.[5,40–42] Most of this increased output of labeled material occurs via the bile and feces, with a relatively small proportion occurring in the urine. Analyses of the bile and urine of Gunn rats and humans with unconjugated hyperbilirubinemia have shown that the pyrrolic material that is excreted in relatively large amounts during phototherapy is made up of two fractions. One fraction contains compounds derived from bilirubin[5,40,41] and the other contains intact unconjugated bilirubin itself.[5,40,42–44] Therefore, the blanching of the skin and the diminution of serum bilirubin levels caused by phototherapy are the result of two distinct processes: (1) conversion of bilirubin to compounds that are readily excreted and (2) enhanced excretion of unconjugated bilirubin. The relative importance of these two processes in humans receiving phototherapy has not been determined, but studies on Gunn rats suggest that each of them makes an important contribution to the effectiveness of the treatment.[5,40] At present, it is not known whether they are independent photobiological processes or whether one depends on the other. Nor is it clear whether they both represent a general photobiological effect on bilirubin in several tissues or, alternatively, whether each reflects the photometabolism of bilirubin in a separate tissue such as the skin or the blood.

Photodegradation of Bilirubin In Vivo

As noted above, phototherapy stimulates the excretion of bilirubin metabolites principally into the bile and to a lesser extent into the urine.[40–42] These metabolites are more polar and water soluble than bilirubin, are mainly diazo-negative, and some of them, particularly those excreted into the urine, show a positive pentdyopent reaction.[40,45,46] Chemical and chromatographic studies indicate that they are similar to the unidentified degradation products of bilirubin that are formed by

Crigler-Najjar patients and Gunn rats even in the dark.[40, 41] On this basis it has been proposed that the principal effect of phototherapy is to stimulate the alternate pathways of bilirubin catabolism that exist normally in subjects that lack an effective mechanism for bilirubin conjugation.[40, 41] This conclusion is, however, probably unjustified since qualitative similarity between the photoproducts and the "alternate pathway" products does not necessarily indicate that they are formed by the same mechanism in each case; indeed, it would be surprising if they were.

None of the bilirubin photoproducts that are formed during phototherapy has been completely identified or isolated in pure crystalline form. As previously described, however, three of them have been formulated as dihydroxytetrapyrroles (figure 6)[24] and others appear to be dipyrroles of the propentdyopent type.[46, 45, 46] From the known photochemistry of bilirubin, it seems most likely that the polar metabolites that are excreted during phototherapy are mainly photooxygenation products of the pigment formed in a self-sensitized reaction involving singlet oxygen. This is compatible with the detection of dihydroxytetrapyrroles and propentdyopents among the products, since these compounds have been shown to be produced by attack of singlet oxygen on bilirubin in vitro. Circumstantial evidence for the role of singlet oxygen in the photodegradation of bilirubin in vivo has been provided by experiments in which chemical photosensitizing drugs were used to accelerate the effect of phototherapy on serum bilirubin levels in the Gunn rat.[5,47,48] Injection of Gunn rats with hematoporphyrin or riboflavin, which are better singlet oxygen sensitizers than bilirubin, followed by phototherapy, caused a much more rapid decline in the serum bilirubin concentration than was observed in control rats treated with light alone.

Both theoretical and experimental considerations suggest that the main sites for bilirubin photooxygenation are the skin and subcutaneous fat rather than the serum. At low oxygen tensions the rate of bilirubin photooxygenation increases with increasing oxygen concentration. Since the solubility of oxygen is considerably greater in lipophilic media than in water,[49] photooxygenation of bilirubin in the skin and fatty tissue would be expected to occur more rapidly than photooxygenation of bilirubin in the serum. In addition, the circulating bilirubin in the serum, which is partially shielded from light by red-cell hemoglobin, is exposed to a smaller proportion of the total dose of light during phototherapy than the more static extravascular bilirubin fraction close to the irradiated surface. The loss of yellow pigmentation from the skin that is commonly observed during phototherapy of jaundiced newborns, spectroscopic measurements on skin biopsy samples taken from infants undergoing phototherapy,[50] and in-vitro studies on the photodegradation of bilirubin bound to skin segments[51] also implicate the skin as an important locus for bilirubin photooxygenation in vivo. Perhaps the most convincing evidence for the photodegradation of bilirubin in skin comes from a recent study of an adult patient with the

Crigler-Najjar syndrome who failed to respond to phototherapy.[45] Although irradiation of this patient had little effect on the serum bilirubin concentration, it did cause a change in skin pigmentation. This change was accompanied by a huge increase in the excretion of propentdyopent-positive material in the urine. The available evidence, therefore, strongly suggests that photooxygenation of bilirubin to lower molecular weight compounds in the skin is a major effect of phototherapy. But because of the lack of experimental data, it is not clear at present whether photooxygenation of bilirubin in the blood also occurs during the treatment.

As previously described, the photooxygenation of bilirubin in hydroxylic solvents is a stepwise process that involves addition of singlet oxygen and leads ultimately to maleimides and propentdyopent adducts via a sequence of higher molecular weight oxygenated intermediates. A similar sequence of reactions would be expected to occur in vivo. However, because the light flux and oxygen concentrations in vivo are lower than those generally used in studies in vitro, and because of competition for singlet oxygen by endogenous metabolites, the photobiological reaction is likely to be slow and may not proceed to completion. In addition, metabolic processes may interrupt the photocatabolic sequence in vivo by removal of the initial intermediates before they are able to undergo further reaction. In this way, compounds that have only a transient existence in the in-vitro photooxygenation experiments might be "trapped out" and excreted in vivo as a consequence of the dynamic nature of the living system.[b] Therefore, water-propentdyopents, methylvinylmaleimide, hematinic acid imide, and the oxygenated derivatives of bilirubin that lead to them are to be expected as photometabolites in vivo. Photooxygenation of the slowly exchangeable bilirubin pool in the skin is more likely to proceed to the colorless propentdyopent stage than photooxygenation of bilirubin in the blood. It may be noted that photodegradation of bilirubin in plasma in-vitro initially gives products that are more polar than bilirubin but that nevertheless bind tightly to albumin and are excreted via the liver when injected into Sprague-Dawley or Gunn rats.[45] On the other hand, more prolonged irradiation of jaundiced plasma gives compounds that bind less tightly to protein and are principally voided in the urine when injected into normal or jaundiced rats.[45]

The rate of degradation of bilirubin in the skin during phototherapy may exceed the rate at which the pigment is transported to the skin from the plasma. For this reason, phototherapy will tend to lose its effectiveness once the skin becomes decolorized even though serum levels of bilirubin remain elevated. It is possible that by increasing the blood flow to the skin, for example by massage or by the incorporation of suberythemal ultraviolet light into the spectrum of phototherapy lamps, the effectiveness of phototherapy might be improved.

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[b] For this reason the photoproducts that are excreted in vivo may be different from those formed on irradiation of bilirubin in vitro. Furthermore, products formed in vivo may undergo metabolic transformation before being excreted. Therefore, a difference between the products that are excreted during phototherapy and those formed in vitro does not necessarily mean that different photochemical processes are involved in each case, as previously suggested.[40]

Photostimulated Excretion of Bilirubin

The second major effect of phototherapy, enhanced biliary[5, 40, 42, 43, 47] and urinary [44] excretion of unconjugated bilirubin is the most puzzling. It is difficult to explain in terms of a photochemical reaction of bilirubin, since overall no covalent bonds are formed or broken, and it is hard to understand how substantial amounts of the unconjugated pigment can cross the canalicular membrane of the hepatocyte. At present there is little experimental evidence to show how phototherapy causes this effect, but several theoretical possibilities may be briefly considered.

One possibility is that light has a direct effect on the liver, thereby altering its normal metabolism. Although light may penetrate to the liver, the intensity would be extremely low and it is difficult to conceive of a photobiological process with a quantum efficiency large enough to have such a marked effect. Therefore, this possibility may be discounted.

A second possibility is that the photooxygenation products formed in peripheral tissues are toxic to the liver, making it permeable to the unconjugated pigment. Such a toxic effect would be expected to alter the hepatic excretion of other compounds as well as bilirubin. Although the excretion of bromosulfophthalein is enhanced by phototherapy,[42] the excretion of several other compounds, including bile salts, cholesterol, phospholipid, protein, or Evans Blue, is not affected.[1] Furthermore, the administration of biliary photoproducts obtained from irradiated Gunn rats to other Gunn rats kept in the dark does not cause enhanced excretion of unconjugated bilirubin.[1] Therefore, the possibility that photoproducts alter the permeability of the cannicular membrane of the hepatocyte is unlikely.

A third hypothesis is that the photoproducts form complexes with unconjugated bilirubin and facilitate its transport through the liver. Complex formation has been invoked previously to explain why injection of conjugated bilirubin into Gunn rats causes a large increase in the biliary excretion of unconjugated bilirubin.[52] There is no evidence to support this hypothesis, and it appears to be ruled out by the observation, mentioned above, that injection of biliary photoproducts does not augment bilirubin excretion in the Gunn rat.[1]

Even in the absence of a functioning conjugating mechanism, small amounts of bilirubin are excreted in the bile of Gunn rats.[52] This fraction increases when Gunn rats are infused with the unbound unconjugated pigment, albeit in large doses.[53] These observations suggest a fourth explanation for the enhanced biliary output of bilirubin during phototherapy. Perhaps photodissociation, or photoisomerization reactions, or even photothermal effects cause the release of bilirubin from tissue binding sites and lead to an increase in the unbound fraction of bilirubin in the serum. This lipophilic unbound fraction might then be able to permeate the hepatocyte membrane to a significant degree. Finally, the possibility must be entertained that the photooxygenation of bilirubin near the skin surface leads to the formation of oxygenated tetrapyrrolic compounds that can be excreted without being conjugated but that are reconverted back to bilirubin either in the bile or during their passage through the liver.

CONCLUSIONS

Recent work on the photochemistry of bilirubin indicates that photooxygenation of the pigment is probably a major process in phototherapy. The complete details of the photometabolism of bilirubin in the jaundiced newborn and the mechanism of phototherapy, however, are still poorly understood. Specific aspects of the problem that merit further study include the following: The identity, toxicity, and mechanism of formation of the photoproducts require elucidation, and it needs to be determined whether the initially formed photoproducts are further metabolized to secondary compounds before they are excreted. Useful information regarding these points might be obtained from in-vitro studies of the photochemical reactions of bilirubin bound to skin, lipid, and albumin.

The mechanism by which light stimulates the excretion of unconjugated bilirubin requires clarification, and the quantitative relationship between photoproduct formation and enhanced bilirubin excretion needs to be ascertained. The major loci for the action of phototherapy should be defined in more detail, and it would be relevant to know whether circulating bilirubin in the blood is involved in the primary photobiological process. Reliable kinetic data for the rate of transfer of bilirubin between serum and skin in vivo are badly needed, and it might be of practical interest to determine whether the rate of exchange and the effectiveness of phototherapy are influenced by photothermal effects within superficial tissues. The possible role of endogenous photosensitizers or singlet oxygen quenchers in phototherapy should also be explored.

Finally, since bilirubin is a photosensitizer, the possibility that irreversible photodynamic damage might occur during treatment demands careful attention. Recent in-vitro studies on the photohemolysis of fetal red cells [54] and the photosensitized formation of cholesterol peroxide in liposomes [55] are reassuring and suggest that photodynamic damage is unlikely to be a real hazard. Further investigation of this point would be welcome, however.

Future work along the lines indicated above should eventually lead to a comprehensive understanding of the mechanism of phototherapy. It is to be hoped that this will also lead to improvements in the practical application of this widely used technique.

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Effect of Light on Bilirubin Binding by Serum

J. Kapitulnik, N. A. Kaufmann, S. H. Blondheim, I. Dudakova,
and Alex Russell

The increasing use of phototherapy for reducing serum bilirubin in neonatal jaundice has drawn attention to its possible effects on biochemical and physiological parameters in jaundiced newborns. Dye-sensitized photooxidation of albumin decreases its binding affinity for bilirubin.[1] A decrease in bilirubin binding affinity of serum was also found in an infant with "bronze" baby syndrome, in whose blood photoproducts of bilirubin had accumulated.[2]

The objectives of the present investigation were to determine whether illumination of serum with visible light changes its binding affinity for bilirubin, whether photoproducts of bilirubin interfere with the binding of bilirubin by serum, and whether light affects on the bilirubin binding affinity of the serum of jaundiced infants undergoing phototherapy.

MATERIALS AND METHODS

Serum from normal fasting adults was illuminated under sterile conditions for 24 hours below a canopy of three, 6-watt, clear white, GE F6T5CW fluorescent lighting tubes. Light intensity at the level of the serum was 780 foot-candles. Bilirubin was added in increasing concentrations, as previously described,[3] to serum that had been illuminated and to aliquots of the same serum that had been kept in the dark for 24 hours at room temperature.

Total bilirubin was determined by the Malloy-Evelyn diazo method,[4] and albumin was determined by the acid-alcohol precipitation method of Fernandez et al.[5] Bilirubin binding affinity was evaluated using a quantitative Sephadex gel filtration method.[3]

Human serum albumin (AB KABI, Stockholm) in aqueous solution was treated with charcoal by the method of Chen [6] in order to remove free fatty acids and other low molecular weight substances. The charcoal-treated albumin solution was then diluted with phosphate buffer (0.067 M (molar) pH 7.45) to a final concentration of 4 grams per 100 milliliters. "430 pigment" was isolated from bilirubin-albumin solutions illuminated with visible light for 24 hours.[7] This pigment, in veronal buffer solution (0.1 M, pH 8.4), was added to bilirubin-albumin or bilirubin-serum solutions.

Thirteen infants with neonatal jaundice underwent phototherapy for 24 hours under an Air-Shields (Hatboro, Pa.) phototherapy unit (model PT-53-1), with eight, 20-watt fluorescent tubes, at a distance of 52 centimeters, which gave a light intensity of 650 foot-candles. Blood was drawn before and after 24 hours of phototherapy. Serum bilirubin and albumin were determined, and the bilirubin-albumin molar ratio was increased to 1.5 in both pre- and post therapy serum samples by addition of bilirubin. Bilirubin binding affinity was evaluated in these bilirubin-enriched sera and compared with that of sera taken from four infants not exposed to phototherapy.

RESULTS AND DISCUSSION

For both illuminated and unilluminated sera, the same amounts of bilirubin were adsorbed by the Sephadex column and eluted from it, at each bilirubin-albumin molar ratio (figure 1). Thus, illumination of the serum did not affect its ability to bind bilirubin under the conditions of the experiment. On the other hand, it should be emphasized that in the infant exposed to light, photooxidation of albumin might occur through the action of photosensitizing agents present in the circulation, with a resultant decrease in binding affinity for bilirubin as postulated by Odell et al.[1]

Although illumination of serum did not affect its binding affinity for bilirubin, we were able to show displacement of bilirubin from albumin or serum when the "430 pigment," a photoproduct of bilirubin, was added to artificially jaundiced bilirubin-albumin and serum solutions. Both bilirubin and "430 pigment" are adsorbed by the Sephadex column from solutions with added "430 pigment," and after elution from the column they are extractable by $CHCl_3$, thus giving optical density values greater than those due to bilirubin alone (unconnected points, figure 2). The "430 pigment" was removed, therefore, from the $CHCl_3$ extract by extraction with veronal buffer, as in the extraction procedure for the isolation of "430 pigment."[7] This veronal extraction leaves only bilirubin in the $CHCl_3$ solution (solid lines, figure 2).

More bilirubin was liberated from charcoal-treated albumin and adsorbed by Sephadex from the bilirubin-albumin solutions to which "430 pigment" was added than from those without added pigment (figure 2). This shows that addition of "430 pigment" leads to a decrease in the bilirubin binding affinity of albumin. This effect, however, was found only at high bilirubin-albumin molar ratios, at which bilirubin is loosely bound to albumin at the binding sites with the higher dissociation constant for bilirubin. The tighter binding of bilirubin at lower bilirubin-albumin molar ratios was not affected by the addition of the "430 pigment."

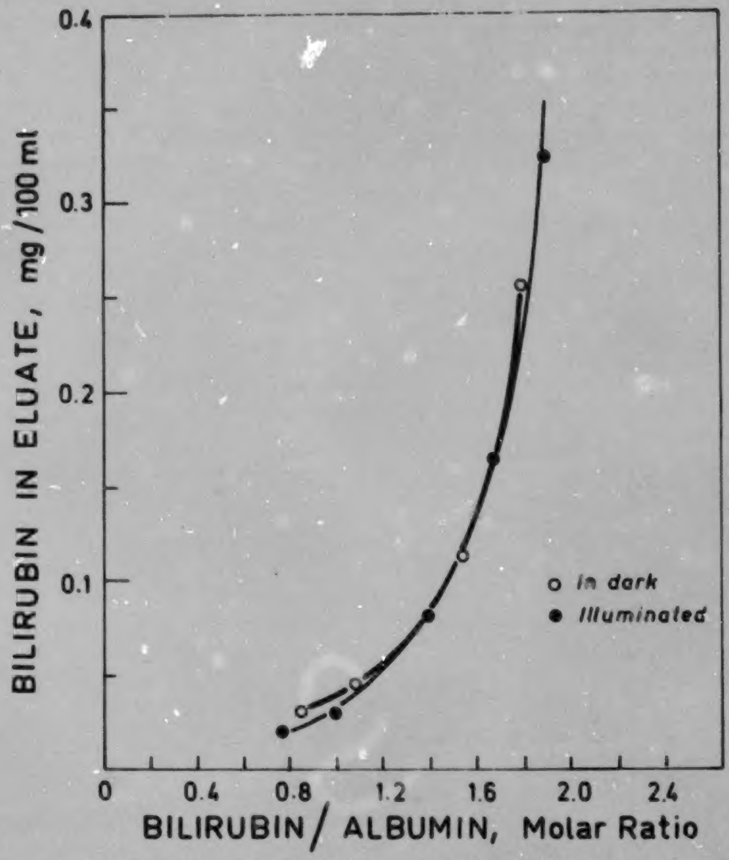

FIGURE 1. Effect of illumination of serum on its binding affinity for bilirubin. Normal adult serum illuminated or kept in the dark for 24 hours. Binding affinity for added bilirubin determined by Sephadex gel filtration.[3]

Similar results were obtained when this experiment was repeated with bilirubin-serum solutions, and again the addition of "430 pigment" decreased the binding affinity of serum for loosely bound bilirubin (figure 3). In the case of serum, however, unlike albumin solutions, the addition of "430 pigment" did cause minimal displacement of bilirubin from the binding sites, which tightly bind bilirubin (figure 3). This difference between albumin and serum may result from the presence in serum of substances that compete with bilirubin for binding to albumin, thus facilitating displacement of bilirubin by "430 pigment." These substances were probably removed from the albumin solution by the pretreatment with charcoal.

The "430 pigment" was found in the ultrafiltrates of illuminated bilirubin-albumin solutions and several of its characteristics were de-

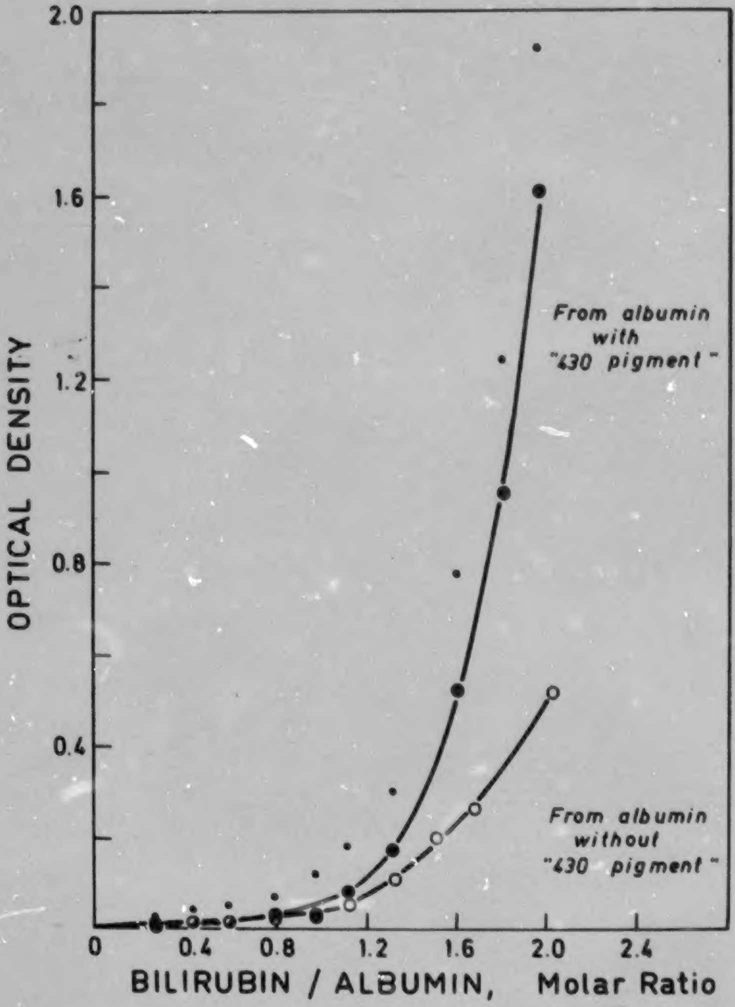

FIGURE 2. Effect of addition of "430 pigment" on bilirubin binding affinity of *albumin*. Optical density represents concentration of pigment(s) in $CHCl_3$ extracts of eluates of Sephadex columns to which bilirubin-albumin solutions were applied. Curves of connected points represent opitcal density after extraction with veronal buffer; unconnected points represent optical density before veronal extraction of extracts derived from bilirubin-albumin solutions with "430 pigment" added.

scribed.[7] Although this pigment is ultrafiltrable, it can be bound to a certain extent by albumin, for when albumin was added to the ultrafiltrate and this solution was ultrafiltered, only traces of "430 pigment" were found in the second ultrafiltrate (unpublished observations).

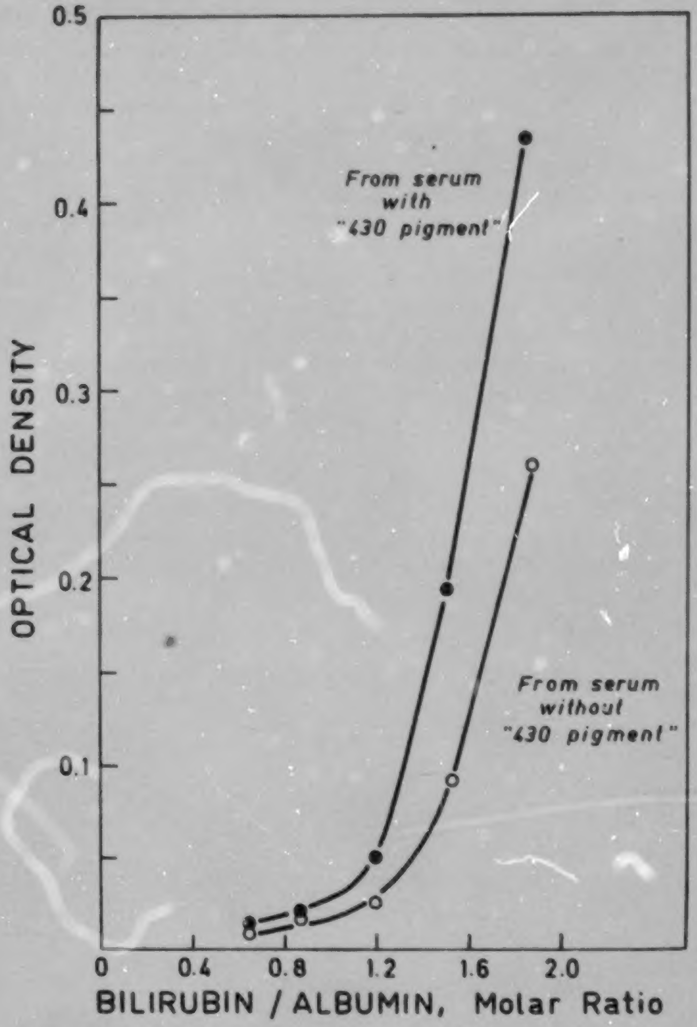

FIGURE 3. Effect of addition of "430 pigment" on bilirubin binding affinity of serum. Optical density after veronal extraction of $CHCl_3$ extracts of eluates of Sephadex columns.

The ultrafiltrable "430 pigment" was also found and isolated from serum, urine, and feces of an infant with Crigler-Najjar syndrome, and increased in concentration during phototherapy.[8] It should be emphasized that significant amounts of "430 pigment" were not found in the serum of jaundiced infants without Crigler-Najjar syndrome who underwent phototherapy, although it was occasionally found in their urine and feces. The

"430 pigment," however, might be present in the serum of cases in which photoproducts of bilirubin accumulate, as has been suggested for the bronze baby syndrome. In such a baby, the bilirubin binding affinity of serum decreased during phototherapy.[3] From the present studies, it appears that the displacing effect of "430 pigment" on bilirubin binding would be of importance only after saturation of the high-affinity binding sites of albumin, which are the first to bind bilirubin.

In order to determine to what extent the findings of our in-vitro experiments apply to the in-vivo situation, we evaluated the bilirubin binding affinity of serum of jaundiced infants who underwent phototherapy. The amount of bilirubin adsorbed by Sephadex at a bilirubin-albumin molar ratio of 1.5 was determined separately for each infant in serum samples obtained before and after 24 hours of phototherapy, and the percentage difference (24 minus 0 hour values) was calculated.

In 9 out of 13 infants the bilirubin binding affinity of serum increased during phototherapy, as indicated by smaller amounts of bilirubin adsorbed by Sephadex after 24 hours of treatment, thus giving a negative difference (figure 4). A similar degree of improvement in bilirubin binding affinity, however, was found in two out of four infants who did not undergo phototherapy during a 24-hour period (figure 4). This improve-

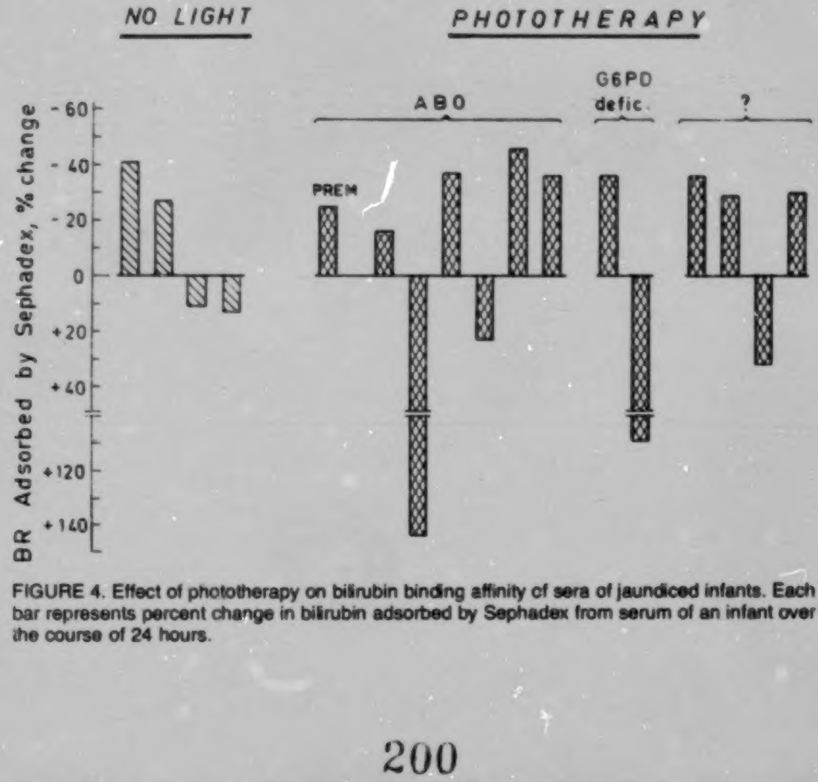

FIGURE 4. Effect of phototherapy on bilirubin binding affinity of sera of jaundiced infants. Each bar represents percent change in bilirubin adsorbed by Sephadex from serum of an infant over the course of 24 hours.

ment in the bilirubin binding affinity of serum, which is much lower in newborns than in adults,[3] begins in the neonatal period.[9] It is evident as early as the third day of life, and after the third month of life[10] the binding affinity approximates that of the adult.

In 4 out of the 13 infants under phototherapy, the bilirubin binding affinity of serum decreased during illumination, and in two of the four, this decrease was marked (figure 4). On the other hand, a decrease in bilirubin binding affinity of serum was also found in two of the four nonilluminated infants, but this decrease was much smaller than that found in the phototreated infants.

These results are preliminary and the studies will be extended to include a larger number of infants in both control and study groups. This is essential in order to determine whether the marked decrease in bilirubin binding affinity of serum found in 2 of the 13 infants who underwent phototherapy may be found in nonilluminated infants as well. Because of the possibility that illumination may reduce the bilirubin binding affinity of jaundiced serum, it appears advisable to monitor the bilirubin binding affinity of serum in infants undergoing phototherapy.

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Discussion

Dr. Schmid: Before beginning the discussion I would like to ask Dr. Plotz to summarize his chromatography studies.

Dr. Plotz: Dr. Scharschmidt, in Dr. Berk's lab, and I have been working on the removal from blood of bilirubin and other albumin-bound substances by a variant of affinity chromatography in which serum albumin is coupled covalently to beads of agarose and blood is then filtered over those beads (*J. Clin. Invest.* 53:778–785; 786–795, 1974).

Substances that are noncovalently linked to albumin, but are in equilibrium with it, like bilirubin, will equilibrate with the albumin that is bound to the agarose. In a nonequilibrium situation in which blood is being passed over such a column, there is a natural tendency for substances to transfer to the gel-bound albumin because the concentration in the serum is always higher than the concentration on the gel that the serum albumin is meeting as it flows through the column. If you pass serum with a lot of bilirubin over a column of agarose-albumin, some of the bilirubin does come through, but a considerable proportion of it sticks and is not further eluted by saline. When you elute that column with 50-percent ethanol, you get quantitative recovery of the bilirubin that has bound. Albumin has to be on the agarose; agarose unlike Sephadex does not have a tendency to bind the hydrophobic bilirubin.

The substances that bind to the albumin that is attached to the agarose are the same substances that bind to the albumin in the serum. In general, the bound albumin seems to behave like normal albumin. Some thyroxin is bound, some cortisol is slowed up by the column, some of the bile salts are more or less tightly bound to the conjugated albumin as they are to the serum albumin. Digitoxin binds strongly to serum albumin and to agarose-albumin gel and digoxin binds to neither.

We have applied these columns to the treatment of hyperbilirubinemia in jaundiced rats in an extracorporeal profusion technique. At the end of the experiment, the column is bright yellow. The bilirubin can be eluted quantitatively from the column and the column can then be reused. It has lost none of its capacity by virtue of the elution. In an experiment in which hot bilirubin was injected into a Gunn rat, its disappearance was determined for 72 hours prior to extracorporeal perfusion of the rat. The column very efficiently removes essentially all of the bilirubin that passes over it in the first pass of blood over the column. The serum bilirubin after an hour's perfusion had fallen from 8.24 to 2.62 milligrams percent. About 1 milligram of bilirubin was recovered from the column, which represents about a fifth of the total body bilirubin of the Gunn rat and close to 100 percent of its serum bilirubin.

In similar studies with obstructed rats, again all of the bilirubin—this now being conjugated bilirubin—was extracted; the bilirubin fell but to a lesser extent for various reasons that I can only speculate on. An equivalent amount of bilirubin has been removed, and this again represents a substantial amount of the bilirubin that is in the rat.

The columns do not do anything very terrible to the formed elements of the blood nor to some clotting factors. In studies with human blood passed over columns in vitro, there are very small changes in the white count and in the platelet count. There probably are more significant changes during in vivo perfusion, which I will not discuss.

What we are doing at the moment is tooling up to apply such columns to two relevant animal models. First, is the newborn monkey, which gets an early hyperbilirubinemia. We want to see whether we can safely remove bilirubin from the newborn monkey as we have from the rat. Then, in an attempt to scale up the method, we hope to do this on newborn sheep, which are very close in size to newborn humans. There are other differences, but I think what we need to do is some scaling up. We are most anxious to have any suggestions about directions that we perhaps ought to pursue.

Since this is a discussion of phototherapy, may I mention that we do have some preliminary experiments that Dr. Berk and John Vergalla have carried out in looking at the photoproducts of bilirubin in bilirubin-containing serum that has been exposed to light. When they take such serum that has been irradiated in vitro or in vivo and at various times after irradiation pass it over these albumin agarose columns so that the albumin is now hopefully competing in the same way that serum albumin is, they find that over the course of the first few hours there is a progressive fall in the amount of bilirubin that sticks to the column. As time goes by, there is an increase in the dializable component of what comes through the column. They have done also, in a very preliminary way, some elution of the columns with the phototreated bilirubin. With progressive elutions in acid and alcohol, you can see quite a number of very nicely colored bands. I think, if I recall correctly, one is green, one is purple, and there are some others that are not colored.

Dr. Ostrow: I would like to ask a question of Dr. Kapitulnik and then make a comment. I am not clear on how you measure the material in the chloroform eluate in your columns. Is this direct spectroscopy at 450 nanometers?

Dr. Kapitulnik: Yes.

Dr. Ostrow: How do you know, then, that you are not measuring "430 pigment," which obviously will not have a sharp peak just at 430 nanometers? There would be some overlap in the 450 nanometer range. Therefore, how do you know that the pigment left on the column is really bilirubin and no "430 pigment" itself?

Dr. Kapitulnik: First of all, if you look at the spectrophotometric curve of the extract before the treatment with veronal you will find the spectrum of the chloroform extract has a peak at about 440 nanometers before extracting it with veronal. After extracting it with veronal, we obtain the peak at 453 nanometers, which is characteristic of unconjugated bilirubin in chloroform. It is a symmetrical peak. If we look at the spectrophotometric curve of the veronal extract, we have exactly the shape of curve that we have when the pigment originally is in veronal. We did not pursue identification further, but I would assume the pigment which remains in chloroform after the veronal extraction is bilirubin since in the case of the serum not containing "430 pigment," the spectrum was the same before and after veronal extraction. In this case we can be pretty sure that it is only unconjugated bilirubin.

Dr. Ostrow: Thank you. My comment has to do with the question that Dr. McDonagh raised, namely why the unconjugated bilirubin comes across in the bile and how is it solubilized? Dr. Flotz described the elution of unconjugated bilirubin from the column with 50-percent ethanol in which it is not normally soluble. I can confirm Dr. McDonagh's comment that the bilirubin that comes out in the bile has the mass spectrum of bilirubin and is not a beta or delta isomer. The two major fragment ions indicate that the propionic acid side chains are on two opposite half molecules and not on the same dipyrrolic half of the molecule.

The question is, How do you break the internal hydrogen bonding that usually suppresses the ionization of the carboxyllic side chains of bilirubin and thus renders bilirubin lipid soluble and not excretable in the bile? One possibility was suggested. There is evidence that the nitrogen groups of the pyrrole rings may be involved in bonding bilirubin to albumin and also in the internal hydrogen bonding of the carboxylic side chains. On the column with the bilirubin bound to albumin, the internal hydrogen bonding may be interrupted so that the bilirubin is not fixed with the carboxylic side chains free, rendering unconjugated bilirubin soluble in polar solvents. Possibly in-vivo bilirubin is complexed similarly with something in the serum that is released by phototherapy. Thus, the complexed bilirubin molecule is oriented in such a way that its internal bonding is prevented and it is now soluble in polar solvents. Alternatively, there is the possibility that bilirubin is rearranged to a different isomer which sterically cannot undergo the internal hydrogen bonding. In Israel we sat down with Dr. Blauer and looked at a molecular model of bilirubin. He showed that the gamma isomer of bilirubin, which you would admittedly not expect to be formed enzymatically, would indeed be unable to bond internally. Therefore, bilirubin might pass into the bile as a gamma isomer and this would not be distinguishable from the IX-alpha bilirubin by mass spectroscropy. One would have to do nuclear mass resonance to make this distinction and we have been unable to do that as yet.

Dr. Kapitulnik: Before giving you the answer, I would like to comment on something that I did not show on the Crigler-Najjar infant. There is something very peculiar. From the serum, feces, and urine, we could extract into chloroform a pigment that was not reextractable into veronal. Into chloroform we extracted both the "430 pigment" and the pigment that was not reextractable into veronal. This pigment, to our surprise, was easily dissolved in methanol. As you know, bilirubin is very insoluble in methanol. This pigment was also diazo-positive; it gave a diazo product with the same spectrum as unconjugated bilirubin. This probably would be in accordance with a possible small change in the bilirubin molecule which increases its solubility in polar solvents.

Dr. Ostrow: The only evidence I have for this is that if one dissolves bilirubin in a chloroform-methanol solution, adds liditic acid (EDTA), and takes the solution down to dryness, one can then dissolve that unconjugated bilirubin residue in a very small volume of water. Maybe EDTA forms a kind of addition compound.

Dr. Schmid: I am not surprised really that Dr. Plotz cannot remove the photooxidation products that he found in the orginal bilirubin. I think that goes back to an observation by Ostrow many years ago that if one irradiates bilirubin in albumin, it becomes more and more dializable as one goes on with the irradiation.

May I ask, Dr. Plotz, why are you so hesitant to use your column on this endangered patient with Crigler-Najjar syndrome?

Dr. Plotz: That has both a practical and a moral answer. The practical answer is that we have not yet scaled up the hardware to do it and we have not yet solved the problem of sterilizing the product. The moral problem is whether one should embark on a therapeutic maneuver in a genetic disease unless one is prepared to do it for a lifetime. We are not at the moment prepared to do it for a lifetime. Maybe we can be pushed but not at the moment.

Dr. Schmid: I would like to ask a question of Dr. Kapitulnik. You have shown slides suggesting that the binding, the first molar binding of bilirubin in the newborn's serum, the cord blood, was less during the first 3 days of life and then gradually increased. Are you implying that this is a change in the albumin or are you implying that this is something that has to do with a competitor for binding? May I remind you that to my knowledge nobody has found a difference between newborn or cord blood albumin and adult albumin as far as I can determine.

Dr. Kapitulnik: I am glad you asked that question. There are two possible factors. Changes in either or both may be responsible for the increase in bilirubin binding affinity of infant serum that occurs during the first 3–4 months of life. These factors are (1) serum albumin and (2) substances in serum competing with bilirubin for binding to albumin.

Miyoshi and his group published a series of papers in which they described several physicochemical characteristics of the albumin they isolated from cold blood serum (Miyoshi et al., *Tokushima J. Exp. Med.*, 13:121, 1966). They found cord blood albumin to be more resistant to alkaline denaturation than that isolated from adult serum. This recalls the increased resistance to alkaline denaturation of fetal, as opposed to adult, hemoglobin. This increased resistance to alkaline denaturation of the cord blood albumin was shown to decrease after birth and to approximate that of adult albumin at about the fourth month of life, very close to the time when the adult pattern of bilirubin binding was reached in our Sephadex gel studies of infant serum.

The results of our studies with Dr. Timos Valaes suggest that the changes in bilirubin binding in serum in the first week of life in Greek infants may very well result from changes in the concentrations of substances competing with bilirubin for binding to albumin, some of which are as yet unidentified. We found that the bilirubin binding affinity increased in the first week of life in term infants only. We did not find it in preterm infants, most of whom were quite sick and remained so for a week or more. In these preterm infants, the factor of illness probably enhances the effect of immaturity on bilirubin binding.

Dr. Zuelzer: Dr. Kapitulnik, if the binding capacity improves in these first few days, that would imply that substances, these hypothetical substances that you have been speculating about, are present in the cord blood but disappear in a few days. Could you give us any further speculation on what that might be? Were these babies delivered from mothers who had any kind of drug during labor?

Dr. Kapitulnik: This is a possibility. I do not have that information at the moment.

Dr. Brown: I wonder, to extend your question, whether Dr. Kapitulnik tested the mothers' binding capacity in comparison to other adults and whether you compared the mothers' values to the babies'? The other question is, Were the prematures and the full-term babies fed the same thing?

Dr. Kapitulnik: No, we did not test the maternal bilirubin binding affinity. I do not know whether there were differences in feeding.

About what these substances may be, I am not aware whether there were special drugs or medications being given to the mother. Injectable Valium has been shown to displace in-vitro bilirubin from albumin. We tested the bilirubin binding in sera of infants whose mothers had been given Valium about 10 minutes before delivery. We did not find differences when we compared this group of infants with another group whose mothers were not given the drug. It is possible that sodium benzoate, which is the displacer injected with the Valium preparation, is very readily metabolized to hippuric acid and excreted.

Dr. Zuelzer: How about salicylates?

Dr. Kapitulnik: Dr. Odell, do you have some idea about it?

Dr. Odell: Salicylates given to the mother are very bizarre because both mother and fetus have salicylates in their circulation. Of course, Hawkins in Canada has demonstrated that there is a transacetylation to one of the amino groups of albumin. Salicylates are a lot more complicated, I think, than passive transfer.

Dr. Gartner: I just wanted to support Dr. Kapitulnik's observation about the maturation of binding. We also have observed progressive improvement in the molar binding capacity somewhere between 60 and 90 days when tested with our fluorescent dye binding technique. We do not understand the mechanism of this.

Dr. Schmid: We should never forget that albumin binds some things so tightly that you cannot really get these off, particularly fatty acids. The other thing of course is that albumin is heterogeneous in terms of molecular aggregation—monomers, dimers, and polymers. Nobody has, to my knowledge, ever really looked at the binding properties of these aggregates.

Dr. Odell: I have one comment to make and that relates to the old studies of Luck (*J. Biol. Chem.*, 162:181, 1946) on how to preserve albumin solutions. What he did instead of using alkaline denaturation was to use heat denaturation, which varied tremendously with the fatty acids he used. The reason I think it would be very difficult to prove the existence of a fetal albumin is that the composition of the fatty acids in the serum of the fetus and newborn are entirely different from those found when you feed the baby cow's milk 4 days later.

Dr. Kapitulnik: Dr. Odell, what would be the case if you remove the fatty acids by charcoal, for example?

Dr. Odell: It does not get them all off.

Dr. Lois Johnson: You mentioned the possibility that a little ultraviolet light would be good because of its dilatory effects on blood vessels. Dr. Lucey mentioned that a wavelength much closer to 400 nanometers is effective in doing this. That would perhaps be more the wavelength we should consider for the baby.

Dr. McDonagh: Dr. Lucey mentioned this to me too. He tells me specifically that 385 nanometers is quite close to the wavelengths that are used. Also, the thermal effects that we heard about yesterday may be due to a similar mechanism. Absorption of infrared radiation may also dilate the capillaries and help transport bilirubin from serum into the skin.

Physical Science Approaches to Problems of Phototherapy

The Physics of Phototherapy

Leonard Indyk

Many of the exciting advances in medicine are being made in those fields that are being investigated by interdisciplinary teams of physicians and scientists from outside the traditional medical disciplines. It is interesting to note that all of the lead authors in the Chicago Conference on Bilirubin Metabolism in the Newborn[1] held in 1969 were physicians. This afternoon an entire session is devoted to presentations by three nonphysicians. Thus we see an example of this cooperation that has come about during the past 5 years.

My first encounter with the clinical use of phototherapy for the treatment of hyperbilirubinemia occurred during a tour of newborn intensive care units in 1970.[2] Since my training in magnetooptics had given me some familiarity with light, I was intrigued by this therapy. I found that in answer to the same set of questions in the 12 units we visited, I was told of 12 different procedures for administering phototherapy in terms of the criteria used for instituting the therapy, the type of fixture and bulb used, the on-off schedule of those who were using intermittent illumination, and the frequency of, and need for, bulb changes. A systematic survey of the literature and recommendations at the time showed that someone, somewhere had used just about every possible combination of bulbs, number of foot-candles, and lighting schedule.

Four years later we find that the situation has become more clearly defined. There is still no agreement on the matter of continuous versus intermittent phototherapy. The blue-light camp and the natural light camp have not come to terms. But from a clinical point of view there does seem to be a consensus on the criteria for instituting phototherapy for hyperbilirubinemia.[3] All of these questions are under intensive investigation by a committee set up by the National Research Council,[4] and it is hoped that this committee will be able to provide a set of useful guidelines for clinical use of phototherapy and point up those questions that remain unresolved and must be the subject of an intensive research effort.[5]

I will attempt to explore in this paper the physics involved in various aspects of phototherapy. From this will emerge a set of questions that will have to be answered by a set of very carefully planned and controlled investigations in animals and humans.

THE ELECTROMAGNETIC ENVIRONMENT

Man is immersed in a sea of electromagnetic radiation that ranges from cosmic rays to long-wave radio waves. We generally pay no attention to most of this radiation since much of it is of such negligible intensity that it probably has no effect on us (radio waves) and some of it cannot be avoided at all no matter how troublesome it might prove to be (cosmic ray showers). We know that all unnecessary exposure to radioactivity and to X-rays is to be avoided. In addition we have learned that certain wavelengths of ultraviolet radiation are quite hazardous. We generally have not minded too much changes in the visible spectrum to which we are exposed, however. It may well be that the only truly suitable and safe visible light spectrum for man is the solar tradition spectrum under which he evolved (figure 1). Yet as long as we wish to have illumination in the absence of the sun, we will have to be exposed to other spectral distributions.

Fluorescent lights have generally replaced incandescent bulbs, which in their turn replaced open flames. Each of these light sources has a visible spectrum that is quite different from that of the sun, yet it is only during

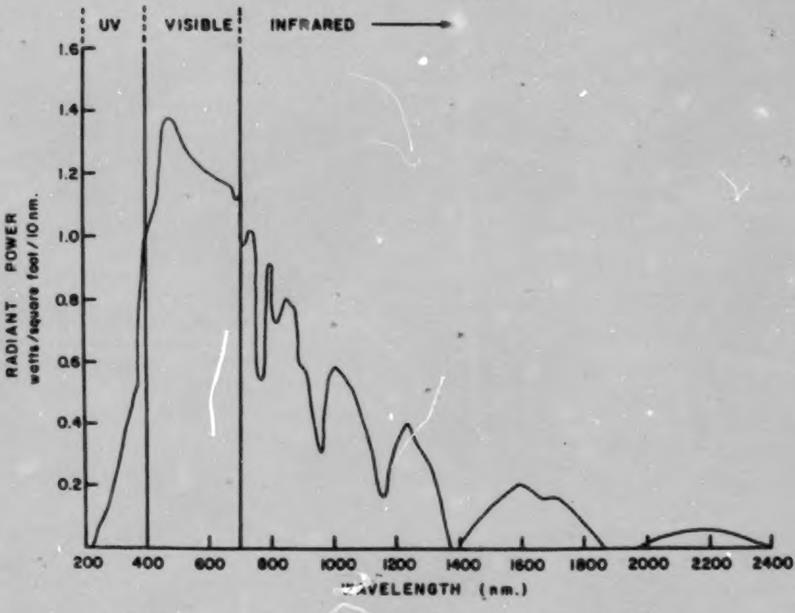

FIGURE 1. Spectral distribution of solar radiant power at sea level.

the last few years that we have become concerned with the possible problems engendered by exposure to a "foreign" spectrum. Part of this is occasioned by the much higher levels of indoor illumination that we find "necessary" and that forces us to subject ourselves to much higher fluxes of nonsolar photons.

A focus of this concern is the newborn who is being treated with phototherapy. His entire body surface, with the exception of his eyes, is subjected to fluorescent light fluxes much in excess of what his parents' head and hands are exposed to. Physicians are justly concerned that there may be long-term side effects of this exposure that will not appear until puberty or beyond. Up to the present time, these concerns are apparently still theoretical.

BASIC OPTICAL CONSIDERATIONS

Light that is incident on the skin can be either totally reflected, partially reflected at the surface with the rest absorbed near the surface, or partially reflected at the surface with the remainder penetrating rather deeply into the underlying tissues. We are here concerned with the light that passes through the skin interface and is absorbed within the first few millimeters of cutaneous tissue. We know that visible light can be used to transilluminate an infant's skull. Hardy, Hammel, and Murgatroyd [6] have determined for adults that the absorption coefficient is about 34 centimeters^{-1} (cm^{-1}) for the outer skin layer (0.4 millimeters (mm) and 8 cm^{-1} for the inner skin (0.4–3 mm). This indicates that the light energy is severely attenuated in the outer few tenths of a millimeter of skin and nearly all of the light is absorbed in this region.

The reflection coefficient for skin has been measured by many investigators using both excised skin samples and in-vivo measurements. The literature has been thoroughly reviewed by Boehm and Tuft [7] who have graphically tabulated the data. They present curves for the maximum and minimum values of reflectance from 0.2 to 2.0 microns for Caucasian and for Negro skin (figures 2 and 3). They also plot the average value for reflectance on the same graphs. (It is interesting to note their comment that in general the lowest reflectance values were obtained with excised skin and the highest values were obtained from in-vivo measurements made on skin from parts of the body rarely exposed to sunlight.) Despite the fact that the data they review is mostly taken on adult skin, the average values agree quite well with the data of Ballowitz and Avery [8] on infants. They found that at 450 nanometers (nm), the reflectance of white infant skin is 25 percent and the reflectance of black infant skin is 10 percent. The absorption coefficient for light black skin is much higher than that for white skin, however. Thus, although only 75 percent of the incident light penetrated white skin as compared with 90 percent for black skin, it penetrated far more deeply. What I have tried to point out here is the error that will be

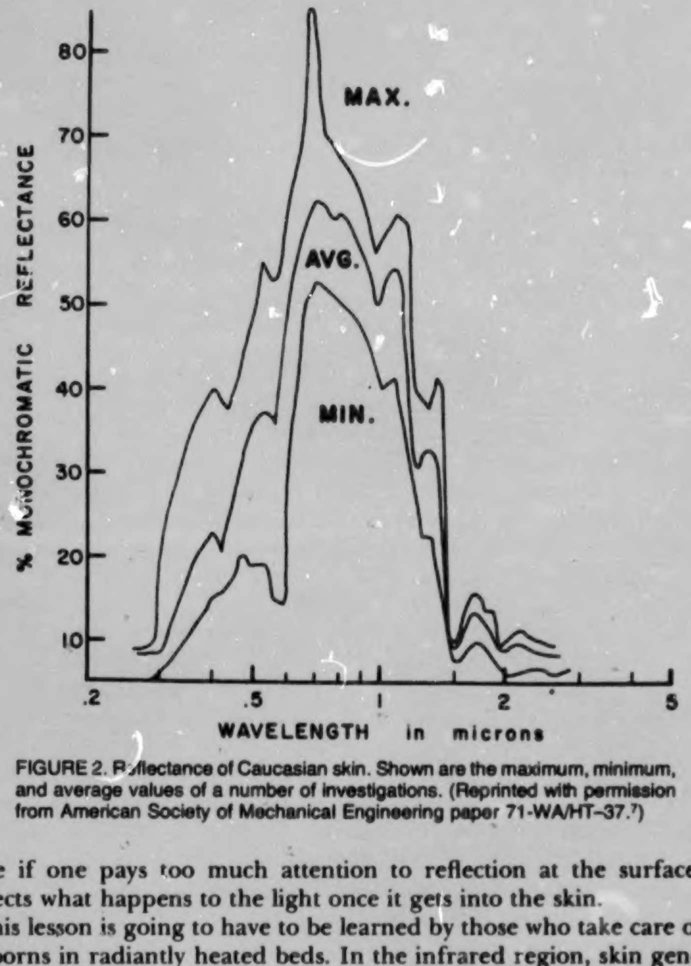

FIGURE 2. Reflectance of Caucasian skin. Shown are the maximum, minimum, and average values of a number of investigations. (Reprinted with permission from American Society of Mechanical Engineering paper 71-WA/HT-37.[7])

made if one pays too much attention to reflection at the surface and neglects what happens to the light once it gets into the skin.

This lesson is going to have to be learned by those who take care of sick newborns in radiantly heated beds. In the infrared region, skin generally behaves like a blackbody,[7] that is, it will absorb almost all of the radiation that is incident on it with negligible reflection. The depth to which the radiation penetrates should determine how effective the heating is. Any evaluation of the performance of one of these units should take into account the detailed spectrum of infrared energy that is employed, and this spectrum does differ considerably from one manufacturer to the next.

In line with this thought, there is a very interesting historical note on phototherapy lights and infant temperature. There have recently been some studies that indicated that phototherapy lights tend to raise the temperature of an infant in an incubator. Some of these effects are obviously due to reradiation by the warmed cover of the incubator, but there is

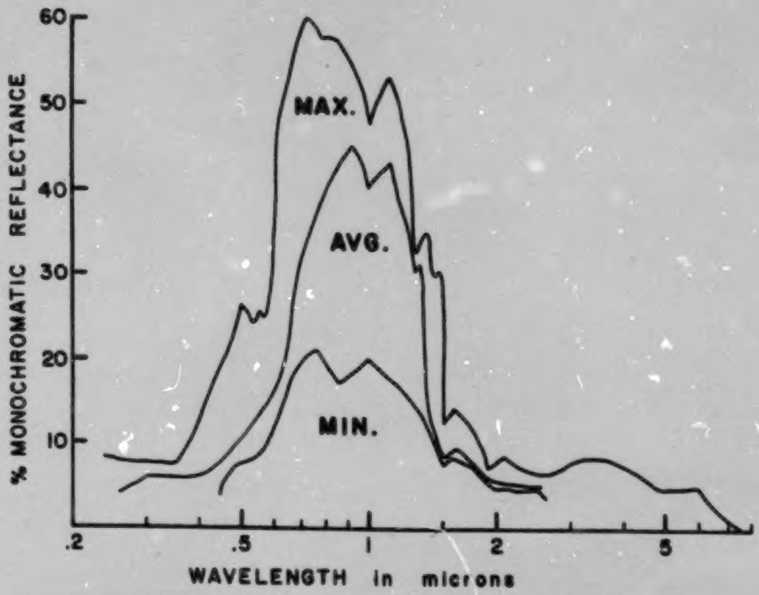

FIGURE 3. Reflectance of Black skin. Shown are the maximum, minimum, and average values of a number of investigations. (Reprinted with permission from American Society of Mechanical Engineering paper 71-WA/HT-37.[7])

also some heating due to direct radiant energy absorption by the skin. Cremer, Perryman, and Richards [9] note that they adjusted the height of their light bank above the infant "to make use of the small amount of radiant heat emitted for keeping the infant's body temperature 98–100 °F" and apparently did not bother about the effect this had on the irradiance in the blue part of the spectrum.

LIGHT—SOURCES AND METERS

The light sources used for phototherapy include daylight and cool-white fluorescent bulbs, a fluorescent bulb with more ultraviolet emission than these two, which renders its output more "solarlike," super-blue bulbs with a very narrow emission band centered about 450 nm, and as reported at this meeting, blue incandescent bulbs.[10] There is no agreement on which bulb source is "better," nor for that matter on the wavelength band or bands that are most appropriate. In an interesting study, Sisson [11] compared the effect in vivo of competing light sources—daylight (F20T12/DA), blue (F20T12/B), and special blue (F20T12/BB) (figure 4). He monitored both the foot-candle illumination and the irradiance in the 420 to 490-nm band. The overall result was that the special blue produced a significantly larger decrement in the serum bilirubin than did the other bulbs. The

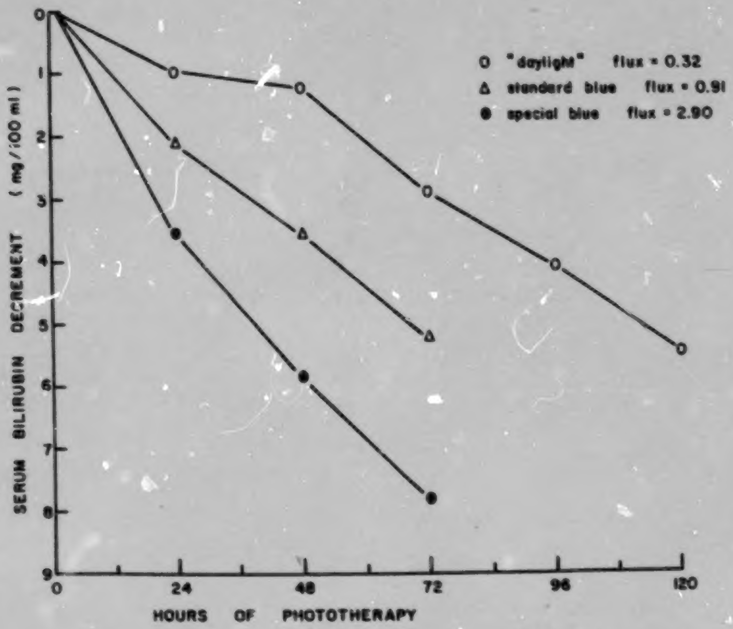

FIGURE 4. Mean decrements of serum bilirubin concentration in each 24-hour period of phototherapy. The effect of each type of fluorescent lamp is shown cumulatively. (Reprinted with permission of the *Journal of Pediatrics*.[11])

"worst" bulb was the daylight source. But this was to be expected since the 420- to 490-nm irradiance provided by the special blue was nine times the irradiance provided by the daylight. Note that the illumination produced by the daylight was about 10 times that of the special blue.

This brings us to the question of how you specify "how much" light is being used in phototherapy. There are least three different numbers that have to be considered here; one is the spectral distribution of the irradiance, the second is the total light dose administered over some arbitrary time interval, and the third may be the maximum value of the light flux over a relatively short time interval.

Irradiance

The irradiance is the light energy flux incident on a unit area of surface within some specified wavelength band. It is usually specified in units such as microwatts per square centimeter per nanometer. The point has been made repeatedly, of late, that the more commonly known and used unit, the foot-candle, is totally misleading when used to describe phototherapy light.[4] The foot-candle measures the amount of illumination falling on a surface as perceived by the "standard eye."[12] It is measured by a meter that has the same spectral response as the human eye. In the measurement by Sisson, et al.,[11] a daylight bulb provided 10 times the illumination, but only one-ninth the amount of "blue-light" energy of a special blue bulb. In almost all of the work that has been reported on clinical use of phototherapy to date, the number of foot-candles of light is the measurement usually reported.

There are tables available that give irradiance distributions for specific light sources provided the number of foot-candles[13] is known. These tables can be used if it is certain that the bulbs used are not aged or otherwise suffer from some form of phosphor problem that would change their spectral output from that specified by the manufacturer for new bulbs. It is generally accepted that if they are not overheated, daylight and cool-white bulbs will maintain better than 90 percent of output over a lifetime of over 1,000 hours with about half of the loss of spectral energy coming during the first 100 hours of operation. It is claimed that the aging of these bulbs is not accompanied by a shift in the output spectrum. This has been shown to be true for Vitalite bulbs[14] and for Panasonic bulbs.[15]

It has also been reported that bulbs placed in a fixture in which the ballast is close to the bulbs overheat and degrade very rapidly. This is a defect that many homemade, inadequately ventilated fixtures suffer. Thus, the uncertainty that occurs if you try to guess the spectral irradiance in the blue portion of the spectrum from the type of bulb, placement of bulbs, reflectance of the fixture combined with the reading of a foot-candle meter or a conventional photographic light meter should discourage one from trying to employ phototherapy with such inadequate data on the light flux.

Total Light Dose

We will make the assumption now that the action spectrum of unconjugated bilirubin in vivo is known. Let us guess that it is a very sharply peaked function that is flat from 450 to 460 nm. This implies that a photon of 451-nm wavelength is absorbed as strongly as a photon of 459-nm light. Biological processes usually do not have such a sharp energy response, nor is the response uniform, but assuming this model will simplify the subsequent discussion.

The total dose of light then is the total number of photons of wavelength 450–460 nm that strike the infant during a specified time interval. Allowing a little bit of sloppiness, the number of photons within the band can be taken as directly proportional to the amount of light energy measured within the band. (The meters that we use for light measurement are usually calibrated in energy units rather than absolute numbers of photons.)

The following irradiation schedules then give the same total dose over a 24-hour period:

- A flux of 60 photons per second administered continuously for 24 hours
- A flux of 120 photons per second administered according to a 12-hours-on, 12-hours-off schedule or any other 1:1 schedule
- A flux of 80 photons per second administered according to a 6-hours-on, 2-hours-off schedule
- A flux of 3,600 photons per flash administered by a strobe light that flashes once per minute for 24 hours

It is difficult to tell why one would choose one of these schedules over any other if there were no information available as to the relative "effectiveness" of these schedules. A search of the literature to date indicates there is no agreement on the effectiveness of different schedules, and virtually every study reported has been the subject of a subsequent exchange of letters to the editor.

Instantaneous Flux Levels

The problem with instantaneous flux levels is that we have very little hard data on the kinetics of the action of phototherapy in vivo. But we do have some provocative information from studies done in vitro. A first question to be answered is whether doubling the irradiance doubles the effectiveness of the light in degrading bilirubin. If that were so, then a graph of the decrease in light absorption by a bilirubin solution as a function of the relative light flux would be linear. This is not the case in vitro.[16] In clinical use of different irradiance levels, there are two pieces of seemingly contradictory evidence. In the comparison study of different light sources that we have already discussed, Sisson et al [11] found that the special blue bulb with nine times the irradiance was 3.5 times as effective as the daylight bulb during the first 24 hours of use as judged by the serum bilirubin decrements produced in his study babies. Over a longer term of 3–4 days, the overall effectiveness of the special blue bulb was only 1.6 times that of the daylight bulb. If you go one step further and take the ratio of the decrement produced over 3 days to the irradiance, then the daylight bulb is seen to be about 5 1/2 times more efficient than the special blue bulb. The group under study included 24 babies for each bulb tested and so there were enough babies so that the data cannot be rejected on statistical grounds. The inevitable conclusion from this is that in vivo, increasing the irradiance does not seem to do much good over a time period that is not usual for the duration of phototherapy. This conclusion is also confirmed by the report of Thaler [17] on long-term use of phototherapy for treatment of Crigler-Najjar syndrome. Despite changing the bulbs used from special blue to regular blue to daylight fluorescent bulbs, he finds that 12 hours of phototherapy under either of the three sources produces the same decrement in the serum bilirubin level.

Isenberg and Fisch [18] have approached this problem from a different point of view. They place an additional bank of bulbs below the naked infant thus irradiating twice the surface area reached by the usual overhead bulbs. They instituted this double-light therapy in the middle of a course of standard phototherapy in which the lights were apparently unable to keep the serum bilirubin concentration from rising to "dangerous" levels. Their data show an abrupt, precipitous drop in the serum bilirubin during the double-light therapy.

There are two possible explanations for this curve beside the speculation that the level was about to turn over and go down and that the double-light merely speeded up the process. One is that over a short term, for a baby with a relatively high bilirubin level, the intensity can be increased and an increased degradation seen, but over a longer time interval, there is not much gain once the irradiance goes above a certain level. The other, probably more tenable, explanation is that doubling the surface area irradiated gives you double the rate of degradation. It is also quite possible that the same result could have been obtained by removing half of the bulbs from the overhead fixture and positioning them below the baby. Thus, the total energy incident on the baby would have been the same, but the area of coverage would have been doubled.

In the exchange of letters that followed Isenberg and Fisch's paper,[18] it was reported that this approach of increasing the light dose that the baby receives had been tried by curving a fixture rather severely (apparently similar to that used by Cremer [9]) and positioning it so that the bulbs were within 3–4 inches of the infant. The babies so treated in a set of paired experiments did indeed exhibit a precipitous decline in serum bilirubin (from 16 to 4 milligrams percent after 12 hours), but this decline was accompanied by very marked irritability and fever. In addition, the baby's temperature could not be controlled unless the light was discontinued.

The effect of phototherapy on peripheral circulation and on insensible water loss are topics of recent research.[20–22] It has been noted that the peripheral circulation increased during phototherapy, and this may prove to be an interesting difference between newborns in closed incubators and open radiant warmers. Since the infrared radiation used in the warmers is quite penetrating, the energy is going to be absorbed in the tissues surrounding the subcutaneous capillary system. Thus local vasodilation and increased peripheral circulation should occur. In addition, since the tissues under the skin where the bilirubin is stored will be subjected to localized heating, it is quite possible that the transport of photoactivated bilirubin or of the intermediate photosensitive material will be enhanced. In fact all processes occurring within the locally heated tissues are probably affected. Thus penetrating infrared radiation may be a very useful adjunct to phototherapy in speeding up the rate-limiting step in the chain of events initiated by the absorption of a photon and culminating in the discharge of the water soluble waste products of bilirubin photodegradation.

"EFFICIENT" PHOTOTHERAPY

The ideal situation in phototherapy probably involves using the very least amount of light necessary. However desirable this seems in theory, it is going to be very difficult to achieve in practice. Some physicians have advocated routine minimal phototherapization of all infants by increasing the environmental lighting in the nursery. The results indicate that this procedure statistically reduces the average serum bilirubin level.[33] At the other end of the opinion spectrum are those who advocate the discontinuance of all phototherapy in view of the possible, presently unknown long-term side effects of the added light. The majority of opinion, as judged by the statistics on use of phototherapy in the United States,[4] holds that phototherapy is a useful therapeutic procedure and should be employed as needed. The serum bilirubin concentration that is used for starting phototherapy is a function of the particular infant's circumstances and the cause of his hyperbilirubinemia, but general guidelines have been promulgated and will probably be accepted.[3,4] These guidelines are based on the cumulated experience of 15 years of worldwide use of phototherapy and not, unfortunately, on detailed knowledge of the precise mode of action of phototherapy.

We have discussed the matter of dose-response elsewhere [34] and will not repeat the details of that discussion. Suffice it to say that the dose-response relationship, even if the absorption coefficient were a constant for all of the subcutaneous tissues, would be very difficult to determine. The response in terms of milligrams percent reduction in unconjugated serum bilirubin must be dependent on the actual concentration of circulating bilirubin, on the concentration stored in the tissues, and on the very dynamic situation involved in the migration of bilirubin between the vascular system and tissue storage. The mathematical expression of this dynamic balance is beyond our abilities at this time due to the paucity of detailed knowledge of bilirubin metabolism in the newborn. As an example of the difficulties, how do you insert a mathematical function into a rate equation to represent the maturing and increasingly efficient liver and enzyme system of the 3- to 4-day-old? The performance of this system probably changes from hour to hour and thus the equilibrium among the various inputs to and outflows from the bilirubin pool is continually shifting.

An additional difficulty was indicated in our previous discussion of total dose. Is it the total dose over 1 minute, 1 hour, or 3 days that is the quantifiable parameter and that can be correlated with changes in the serum bilirubin? Is it better to flash a very intense stroboscope light periodically and then wait for the outmigration of photoactivated bilirubin molecules from the binding sites, or should we stick to a 6-hours-on, 2-hours-off schedule, or continue with continuous phototherapy? I do not think that we will be able to provide a definitive answer to this problem until we get some other method of monitoring the circulating bilirubin other than once every 12-hour sampling. This is a study that can be done in Gunn rats, that most convenient animal model, thoroughly and rapidly.

CONCLUSION

Progress in the clinical use of phototherapy can be traced by an examination of the method of reporting the light used. The initial reports noted that light in the visible region can be used to effect a reduction in serum bilirubin levels. Then it was reported that light from specific bulbs in a specific holder can be used to effect a reduction in serum bilirubin levels. Next it was noted that light from specific bulbs with a specific foot-candle level at the baby can be used to effect a reduction in serum bilirubin levels. Recently, it has been reported that light from specific bulbs providing a visible light flux of a certain number of milliwatts per square centimeter can be used to effect a reduction in serum bilirubin levels. Now we are at the level of sophistication of reporting that light with a specific spectral irradiance measured in milliwatts per square centimeter per nanometer can effect a quantifiable reduction in serum bilirubin levels. Thus the accumulated clinical experience has enabled us to cone in on the appropriate wavelength distribution. The factors of intensity and total flux that would enable us to determine the correct dose-response relationship are still relatively unknown, however. Let us hope that in the various individual and collaborative studies on clinical and research uses of phototherapy now in progress, the measurements of the electromagnetic radiation incident on the subjects will be recorded with the level of sophistication we now know is needed in order to provide correct, quantifiable answers to the questions that are presently unanswered.

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On The Dynamics of Phototherapy

Thomas P. Vogl

In the years since Cremer, Perryman, and Richards[1] first suggested phototherapy for the control of neonatal hyperbilirubinemia, the evidence that it is a successful modality for the control of this condition has mounted;[2–7] today, there can no longer be any question about its efficacy. Several independent estimates indicate that 8–10 percent of all infants born in the United States are presently being treated with light therapy. In view of this extensive use, it is disturbing that so little is known about the mechanisms involved and the optimum manner of administering this therapy. Currently, the light exposure used is determined primarily by how many fluorescent tubes can be fitted around the infant and still permit access; that is, as much light as possible is applied, usually continuously except for necessary nursing care.

Short-term relatively benign side effects of phototherapy have been reported,[8] for example, an occasional rash and loose stools. There has been no epidemiologic studies of large groups to investigate possible long-term morbidity. The period of extensive use of phototherapy has been relatively brief, and such a study would not be complete at present, even if it had been undertaken when this therapy was first introduced. Only the first cohort of such a study would now be reaching child-bearing age.

Visible light is all about us, and we therefore assume, quite naturally, that it is unlikely to have ill effects upon humans. Some evidence is beginning to accumulate, however, to indicate that light, like almost everything else in our environment, is a two-edged sword. Light, of the wavelengths and irradiances used in phototherapy, has the capacity of damaging a number of cellular systems as a result of photochemical reactions, many of which are sensitized by endogenous or exogenous compounds. Visible light inhibits growth and respiration in a number of biological systems by inactivating some of the cytochromes of mitochondria.[9] Recently it has been found that it inactivates purified DNA[10] and kills bacterial cells[11] and that 365-nanometer (nm) radiation inhibits one of the dark repair mechanisms by which bacteria repair damage to their DNA.[12] Bacteria that are repair deficient are much more mutable by ultraviolet light than are wild type cells.[13] There are, in addition, many genetic effects of photodynamic action,[14] and blue light is as effective in making mutations in *E. coli* as is

365-nm light.[15,a] In human infants, melanocyte production is increased significantly by the light usually used for phototherapy.[16]

These considerations are not advanced to suggest that the use of phototherapy be discontinued. It is obvious that such a useful modality should, rather, be explored in greater depth that it has been. It would appear prudent, however, to minimize the exposure of the infant consistent with adequate therapy. It is to this end that the following analysis and speculation is presented.

THE ACTION OF PHOTOTHERAPY

From the available evidence it appears that two separate and distinct phenomena occur when an infant (or Gunn rat) is exposed to phototherapy. One is the breakdown of bilirubin into mono- and dipyrrholes (which are water soluble); the other is the appearance in the bile of unconjugated bilirubin. Let us consider the evidence for these two phenomena.

Ostrow[17] reports that under phototherapy, Gunn rats excrete labeled bilirubin in two roughly equal fractions: (1) unconjugated bilirubin, excreted at rates comparable to the output of conjugated bilirubin in the bile of normal nonjaundiced rats, and (2) water soluble bilirubin derivatives, chromatographically identical with those found in Gunn rat bile under control lighting conditions but different from the products of photodecomposition of bilirubin in vitro. Lund and Jacobsen[18] performed studies on jaundiced infants and observed increased output of unconjugated bilirubin into the bile. Davies and Keohan[19] confirm the results that the immediate photodecompositon products of bilirubin in vivo and in vitro are markedly different, using the method of absorptance difference spectrophotometry. On the other hand, Berry, Zarembo, and Ostrow[20] found three bilirubin derivatives in the Gunn rat that are chromatographically and spectrally indistinguishable from some in-vitro photooxydation products and proposed a singlet oxygen pathway for their generation. Weiss and Rosanelli,[21] using a quantitative chromatrographic-spectrophotometric method with nanogram sensitivity for unconjugated bilirubin, found that free bilirubin is present in the urine of jaundiced (Rh-sensitized) infants born prematurely or at term; this excretion is significantly increased after phototherapy.

Callahan et al.,[22] studying two children with Crigler-Najjar syndrome using tracer methods, present direct, in-vivo evidence for the conversion of bilirubin into diazo-negative compounds.

These and other researchers therefore present copious evidence of the presence of both phenomena in vivo.

Approaching the problem differently, Rubaltelli and Carli,[23] using spec-

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[a] I am indebted to Dr. R. Setlow for the preceding seven references.

trophotometric analysis of skin extracts obtained by biopsy before and after phototherapy, showed that the cutaneous bilirubin concentration dropped 60 percent while the serum bilirubin concentration dropped only 20 percent. Further, they show that under normal conditions, the skin bilirubin level is proportional to the plasma level. After phototherapy, the concentration gradient is increased between blood and skin. They also confirm that light speeds up the formation of water-soluble, diazo-negative derivatives. Vogl[24] observed the effect of opaque patches on the skin of infants under phototherapy and found that the patched area was clearly delineated with the skin being bleached of bilirubin in the exposed areas and jaundiced under the patches. The demarcation was very narrow, often as narrow as 1 or 2 millimeters, indicating that there is little lateral migration of bilirubin in the skin. When phototherapy was discontinued, a time interval of 2–4 hours was required before the skin color again became uniform. This strong binding of bilirubin by the skin is confirmed by the Kapoor and Krishna Murti[25] studies that show that epidermal segments of the three mammals studied can pick up bilirubin from the medium when the bilirubin is present either in the free form or the bound form. The major part of the uptake is, however, as free (unbound) bilirubin. The major part of free bilirubin picked up by epidermis goes into a tight binding with, presumably, the lipoproteins of skin.

From these considerations, the following significant facts stand out:

1. Under phototherapy, bilirubin is excreted into the bile both as diazo-negative water-soluble decomposition products and as "unconjugated" bilirubin.
2. The skin plays an important role in the phototherapeutic process and is a principal site of action for the photons.
3. Bilirubin is tightly bound in the skin and the exchange time constant between serum and skin is significant, approximately 3 hours.

What conclusions can be drawn, what questions posed, and what suggestions made regarding clinical phototherapy from these facts?

The first of these facts appears to allow for two explanations that will have to be distinguished experimentally: (1) There is one site for phototherapy (presumably the skin) and the photocatabolic products generated depend on physiologic factors such as degree of oxygenation, pH, etc., which determine the possible photoactivated pathways and the ratio of the concentrations of products. (2) An alternative explanation is the presence of more than one site for the action of light, for example, the skin and the vascular bed. Particularly in infants, whose skin has a high light transmission compared to adults, sufficient light penetrated the skin to reach the vascular bed without difficulty. In this case, it may well be that one set of photoproducts are generated in one site and the other type in the alternate site. Only future experiments can define the true situation.

An interesting question arises with regard to the findings that unconjugated bilirubin is excreted into the bile under phototherapy. Either, in addition to removing bilirubin from the skin the light penetrates the body cavity sufficiently to act directly on the liver in some totally undetermined manner so as to cause it to excrete unconjugated, water-insoluble bilirubin, or the light acts on the bilirubin in some manner to alter it sufficiently so that the liver can excrete it via a different pathway, or the light produces some chemical that stimulates the liver to excrete unconjugated IX-α bilirubin. No evidence is available to choose between these alternatives, but I submit that the second of these possibilities appears the most plausible. (The first of these could be verified, but has not to date, by shielding the liver from direct radiation by a suitably placed opaque patch.) There are two mechanisms, both confirmed in vitro, that would alter the bilirubin molecule sufficiently for alternate pathways in the liver to become available. These are photoadduction [26,27] and photoisomerization.[28] In either of these cases we visualize the mechanism to consist of photoreaction, which takes place in the skin (or possibly the vascular bed). The altered molecules are transported from the site of phototherapeutic action to the liver where they are excreted into the bile by mechanisms that may differ from those used for the excretion of the IX-α isomer. There the isomers would certainly give a positive reaction for unconjugated bilirubin. The adducts might also give a positive reaction or the adducts may be split from the bilirubin either in the final stages of excretion, or by the pH of the bile, or by the chemical processes used to analyze the bile in vitro. This theory has the advantage of postulating no new mechanisms in the liver but concentrates on the effect of the light on the bilirubin.

IMPLICATIONS FOR CLINICAL PHOTOTHERAPY

Possibly of immediate consequence to the clinical application of phototherapy is the observation [24] of the time constant of several hours for the migration of the bilirubin to and from the skin from the vascular space. The fact that extravascular bilirubin comprises a significant portion of the total bilirubin pool is indicated by the early rise in serum bilirubin following exchange transfusion, a process also requiring several hours, as well as by the studies on rats.[29,30]

Let us examine the dynamics of this process. We know that the migration time constant is about 3 hours. We also know that the effect of phototherapy on the skin is localized laterally so that the light interacts with bilirubin in the skin in the outermost 1 or 2 millimeters of the skin.[24] Therefore, the following three steps have to occur:

1. Bilirubin migrates from the vascular space into the skin. The time constant is about 3 hours. (Leaving albumin in the serum to transport more bilirubin?)
2. The light must interact with the dermal bilirubin. The time constant is probably 10^{-9} seconds.

3. The results of the photochemical reaction must diffuse from the skin back into the circulation for elimination. The time constant is unknown, but probably not longer than step 1.

For phototherapy to be effective in reducing dermal bilirubin, it is necessary that two conditions obtain: first, that light of the appropriate wavelength is incident on the skin and can penetrate to the dermal sites; second, that a bilirubin molecule is present at that site. If no bilirubin is at the site, the light is at best useless and at worst available for causing undesirable side effects.

Since, under phototherapy, as currently practiced, the infant's skin becomes and remains thoroughly bleached, it is clear that the light energy applied is not being used very effectively, since there is little bilirubin in the skin with which the light can interact under these conditions. That is, as an infant is placed under phototherapy, his skin is well loaded with bilirubin and the light applied is maximally effective. After several hours the skin is bleached and the light is only marginally useful (provided that the light-bilirubin interaction occurs primarily in the skin).

From the point of view of the dynamics of the situation, the light would be optimally employed if it were turned on until the skin bilirubin concentration fell to a level about 30 percent above where it would stabilize under continuous lights. The lights could then be extinguished until the skin levels rose again to 70–85 percent of their value under no illumination, and this cycle repeated.

Unfortunately, no detailed data of the time constants or rate of skin bilirubin decrement is available. We are currently trying to establish these parameters in a series of experiments.

In the interim, taking into account the known 2–4-hour limiting time constant and the practicalities of the nursery situation, we would recommend to those clinicians concerned with minimizing the exposure of the infant to phototherapy that they try the following regime: for infants on 4-hour feedings, 2 hours of light followed by 2 hours of dark; for infants on 3-hour feedings, 1½ hours of light followed by 1½ hours of dark.

I believe that this protocol will result in essentially the same serum bilirubin decrements currently obtained under continuous phototherapy while reducing the exposure of the infant by one-half, but I emphasize that this is a suggestion based on theory and not on published experimental data.

FURTHER CONSIDERATION

The increasing popularity of infrared radiant heaters for routine use in temperature control of infants is a complicating factor that should be kept in mind. These radiant heaters as well as phototherapy as currently practiced[31,32] change the peripheral circulation and insensible water loss of infants. Much of this effect is in the skin, where the light is interacting with the bilirubin. Such increased peripheral circulation may well reduce the time constant for the migration of bilirubin into the skin. Reduced water content of the skin could easily effect either the transport of bilirubin into the skin or the transport of photoproducts back into the circulation. Whether these effects would enhance the efficiency of the light in reducing serum bilirubin or reduce it remains to be determined. It would be prudent, however, to separate groups of infants in phototherapy studies depending on which method of maintaining body temperature is employed.

SUMMARY

We have attempted to draw together some of the meager information available on the mechanisms and dynamics of phototherapy in order to see whether the currently employed regimes for phototherapy are optimum. Recognizing the need for much more quantitative as well as qualitative data, we nonetheless can draw the tentative conclusion that continuous phototherapy is not optimum if the aim is to achieve maximum serum bilirubin decrement together with minimum necessary exposure. To this end, based on minimal data and some tentative assumptions, we recommend the trial of a regime consisting of alternate periods of phototherapy and rest, each lasting from 1½ to 2 hours. In the process of reaching these tentative conclusions, we have pointed out some specific areas where more research is vitally needed before a sound regime, based on factual knowledge of mechanisms, sites, and physiology, can be developed.

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Radiometry and Dosimetry as Applied to Phototherapy

Robert J. Anderson

The safety and efficacy of phototherapy for the treatment of neonatal jaundice depends to a large extent on the ability of both the researcher and clinician to accurately measure and quantify the external radiation treatment of the body sufficiently to permit the therapy performed at different times and different places to be compared. In addition, the development of a meaningful dose-response relationship for the in-vivo photodecomposition of bilirubin may permit the administration of accurate phototherapeutic dosages of light, thereby minimizing the potential for deleterious side effects while simultaneously maximizing the benefits of phototherapy.

That these two goals are desirable is obvious. At the present time, however, only the most qualitative judgments may be made concerning phototherapy. Indeed, despite its extensive use in this country for over 5 years, the only conclusions that can presently be drawn are the following: [1,2]

- Phototherapy does result in decreased levels of serum bilirubin.
- Phototherapy does not appear to be implicated in any obvious deleterious effects.

More quantitative assessments of the safety and efficacy of phototherapy await the introduction of more suitable methods for the measurement of the light used.

The question now arises: What characteristics of the light used in phototherapy do we actually wish to measure? The answer to this question is simply, those characteristics that may be related to evoking some biological response. Thus, given the present state of knowledge regarding phototherapy, we would wish to catalog the entire exposure history of each baby subjected to this form of treatment, the exposure history containing records of irradiance within each wavelength interval through the ultraviolet, visible, and infrared portions of the spectrum and including a record of the total duration of exposure as well as any variation in exposure as a function of time.

That obtaining and keeping such exposure records is inappropriate is obvious. Not only would the instrumentation be expensive, but the physician and clinical staff would become involved in making time-consuming measurements that would not relate directly to the well-being of the patient. Finally, the magnitude of the record-keeping job alone would be enormous, with each patient's record including an enormous amount of data that would have to be collated, stored, and ultimately reviewed.

An alternative approach would be a series of measurements, using special-purpose instrumentation designed for simplicity and ease of use, to determine the irradiance of the baby in certain broad spectral bands. Presumably one of these bands would be chosen to represent the spectral region most effective in photodecomposing bilirubin, while the other bands would be chosen to assist in characterizing the total exposure history of the patient.

Further simplification could be achieved by using a single species of fluorescent lamp for phototherapy, so that conversion of the irradiance over one wavelength interval to that over another interval could be simply accomplished. Thus both the exposure history and the irradiance effective in phototherapy could be ascertained from a single, simple measurement.

CONCEPTS OF RADIOMETRY AS APPLIED TO PHOTOTHERAPY

Quantitative assessment of exposure to light during phototherapy depends not only on the use of appropriate instrumentation, but also on the expression of results in appropriate units and on the use of a consistent and unambiguous terminology. The terminology and units typically used in the measurement of light are frequently confusing and inconsistent, so we shall attempt to review here that terminology that is most appropriate for use in describing the practice of phototherapy.

The basic quantity of electromagnetic radiation is the radiant power traversing a surface. This power flow is called the radiant flux, ϕ, and is expressed in units of watts. The radiant flux impinging on a unit area is called the irradiation or irradiance of that area and is expressed by the symbol E, with units of watts per square meter. The total exposure to radiation impinging on a unit area is the time integral of the irradiance and is measured in watt-seconds per square centimeter or joules per square centimeter.

When the variation in a radiometric quantity as a function of wavelength is expressed, the process is called spectroradiometry. For example, the spectro-radiometric analog of irradiance is the spectral irradiance and is defined as the ratio of the irradiance over a given spectral interval, divided by the width of the interval, or $dE/d\lambda$, and is therefore expressed in watts per square centimeter per nanometer. This quantity is only defined for very narrow wavelength intervals, however, and is therefore not applicable to instruments using filters that pass relatively broad spectral bands, as is the case in phototherapy-monitoring instruments using filters.

The irradiance effective in producing a phototherapeutic effect may be defined as the dosage rate, while the time integral of this irradiance, becomes the dosage. The dosage rate, expressed by the symbol E_B, is an average irradiance, weighted by the action spectrum, $k(\lambda)$, defined by the photodecomposition of bilirubin in vivo, as shown in equation 1:

$$E_B = \langle E \rangle = \frac{\int E_\lambda(\lambda) k(\lambda)\, d\lambda}{\int k(\lambda)\, d\lambda} \tag{1}$$

where $E_\lambda(\lambda)$ is the spectral irradiance incident on the baby. The dosage, H_B, is the time integral of equation 1, or:

$$H_B = \int_{\Delta t} E_B\, dt \tag{2}$$

The dosage and dose rate are directly related to the photodecomposition of bilirubin and are therefore the quantities of biological significance.

Table 1 summarizes the radiometric quantities discussed in this section, as well as their units and definitions.

TABLE 1. *Radiometric quantities used in phototherapy*

Quantity	Symbol	Unit	Description
Irradiance	E	W/cm²	$\left[\lim_{\Delta\lambda \to 0} \Delta E/\Delta\lambda\right]_\lambda$
Spectral irradiance	$E_\lambda(\lambda)$	W/cm²/nm	
Exposure	H	Wsec/cm²	$\int E dt$
Dosage rate	E_B	W/cm²	$E_B = \int_{\Delta\lambda} E_\lambda(\lambda) d\lambda$
Dosage	H_B	Wsec/cm²	$H_B = \int E_B dt$

Note.—W = watt, cm² = square centimeter, nm = nanometer, Wsec = watt second.

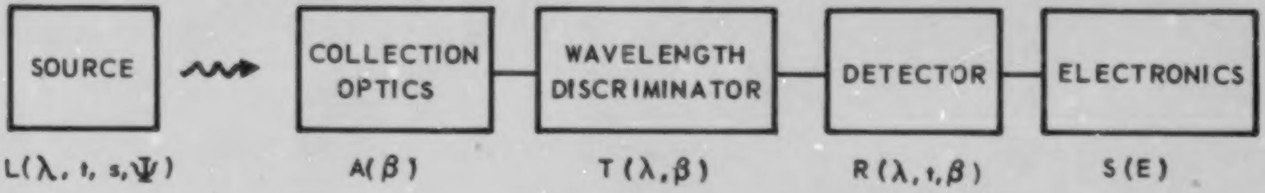
INSTRUMENTATION FOR RADIOMETRY AND DOSIMETRY

The basic problem of measuring the dosage, or the dosage rate, is one of obtaining a signal that is proportional to the weighted average and is independent of the other system variables such as the nature of the light source, detector, or other components. Figure 1 is a block diagram of a basic radiometer including the light source, collection optics, a wavelength discriminator that may be either a filter or a monochrometor, a detector, and the signal-processing electronics. The signal, S, obtained at the output of this device is of the form of a weighted average as shown in equation 3

$$S = \frac{\int_{\Delta\lambda} E_\lambda(\lambda) A(\beta) T(\beta,\lambda) R(\lambda,\beta)\, d\lambda d\beta}{\int_{\Delta\lambda} A(\beta) T(\beta,\lambda) R(\lambda,\beta)\, d\lambda d\beta} \tag{3}$$

where A is the effective area of the receiving aperture, T is the transmittance of wavelength discriminator, R is the responsivity of the detector, and β is a variable describing the angular dependence of these functions.

If the angular dependence all occurs in the collection optics, the integration over the angular variable β may be made, and equation 3 easily reduces to


SOURCE
COLLECTION OPTICS
WAVELENGTH DISCRIMINATOR
DETECTOR
ELECTRONICS
L(λ, t, s, Ψ)
A(β)
T(λ, β)
R(λ, t, β)
S(E)

$$S = \int E_0 A(\beta) T(\lambda, \beta) R(\lambda, \beta)$$

FIGURE 1. Block diagram of the basic elements of a radiometer, including a source of radiance, *L*, impinging on a receiving aperture of area *A*, followed by a filter of transmittance *T*, and detector of responsivity *R*. The output signal *S* should be a function of only the irradiance *E* of the aperture, but is actually given by the integral beneath of the block diagram. The variables are wavelength λ, time *t*, area *s*, solid angle ψ, and solid angle *β*.

$$S = \frac{\int_{\Delta\lambda} E_\lambda(\lambda) T(\lambda) R(\lambda)\, d\lambda}{\int_{\Delta\lambda} T(\lambda) R(\lambda)\, d\lambda} \tag{4}$$

Inspection reveals that equation 1 and equation 4 are identical, subject to the requirement that the product of the transmittance, T (λ), of the radiometer and the detector response, $R(\lambda)$, is identical to the action spectrum, $k(\lambda)$, for the photodecomposition of bilirubin, that is,

$$k(\lambda) = T(\lambda) R(\lambda) \tag{5}$$

Thus to measure the dosage, or dosage rate, requires a filter-detector combination that responds to light in a manner analogous to the in-vivo photodecomposition of bilirubin. Unfortunately, however, the in-vivo action spectrum of bilirubin is not well established at this time, and it is doubtful that it can be well defined since various factors cause it to differ from individual to individual. The fact remains, however, that it is necessary to define, even if arbitrarily, a standard action spectrum to permit the development of suitable instrumentation for performing accurate dosimetry during phototherapy. If such a standard is well defined, then instruments made by different manufacturers may be expected to agree to within the limits of the instrumental errors, probably to within 20 percent. In the absence of a standard action spectrum, the mismatch between detector response functions for different instruments may cause disagreements of as much as factors of two or three or more, as is evidenced by the disagreements between data reported in the phototherapy literature.[3,4]

A possible standard for establishing the response function of radiometric instruments used in phototherapy would be the absorption spectrum of bilirubin in chloroform. This solution is easily obtained and is reasonably reproducible so that it could be used by manufacturers to establish a spectral curve for the response function of their phototherapy monitoring instruments.

It is apparent, then, that a major difficulty in obtaining consistent data between investigators has been the use of a variety of measuring instruments incorporating filters that do not have identical, or even similar, response functions. Additional, and, in some cases, even more significant, errors have been caused by the use of apparatus and techniques that are inappropriate for the measurement task at hand.

Basically, the measurement of light in phototherapy involves two measurements: the first being a calibration measurement, to obtain the denominator of equation 5, while the second is the actual measurement of the phototherapy light source. The quantity of interest is then the ratio of these two measurements.

The problem is that there are three different light sources that this approach must be capable of measuring.[5–7] These are shown in figure 2 and include the following:

- Typical "daylight" fluorescent lamp
- The sun
- A typical 60-watt incandescent lamp

The first two of these may contribute significantly to the exposure of the infant during phototherapy, while the 60-watt incandescent lamp is typical of the light sources used to calibrate the phototherapy monitoring instrumentation. Two problems are obvious from these spectra: first, the dynamic range of irradiances over which the instrumentation is capable of measuring must be large since the irradiance of a 60-watt tungsten lamp in the 400- to 500-nanometer (nm) region is much smaller than that due to either the typical phototherapy light source or the sun; and second, the spectral distribution of these three sources is enormously different, so that the filter-detector combination that is used must be incapable of responding to any irradiance in the region beyond 500 nm. This is particularly significant in using a tungsten lamp for calibration since the output in the near infrared is enormous and the emission maximum occurs at approximately 1 micron.

It is apparent, therefore, that in selecting a radiometric instrument for use in monitoring the dosage rate during phototherapy, a great deal of care must be exercised in selecting an instrument with both a suitable detector,[8] and an appropriate filter. It is especially apparent that broad band radiometers, designed for use in the near infrared region as well as the visible, are not necessarily appropriate for use since their broad spectral response places strenuous requirements on the ability of the filter to block wavelengths other than those in the bilirubin activation band. Figure 3 shows the relative spectral response of the several commonly used detectors for radiometric purposes. It is obvious that the commonly used silicon photodiode detector is not best suited for work in the region appropriate for phototherapy, due both to a large near infrared response that corresponds to the peak emission from a tungsten lamp, as well as a relatively poor response in the region of 400 to 500 nm. The cesium-antimony vacuum photodiode provides a nearly ideal spectral response for use in phototherapy.

Vacuum photodiodes have been largely ignored in this type of application, however, due to the requirement for a bias potential that is usually as large as 180 volts. Studies in this laboratory indicate that such high bias potentials are not only unnecessary, but also undesirable. Figure 4 shows the sensitivity and dark current of a typical cesium-antimony photodiode as a function of bias potential. The diode is a commercially available RCA IP42, and it may be seen that the sensitivity reaches nearly its plateau value with a bias potential of only 15 volts, which is a typical potential available with solid state measuring instrumentation, and is therefore quite reasonable. More importantly, the dark current remains relatively low in this region, and since the predominant source of noise in this type of measurement is dark current fluctuation, the signal-to-noise ratio is extremely high

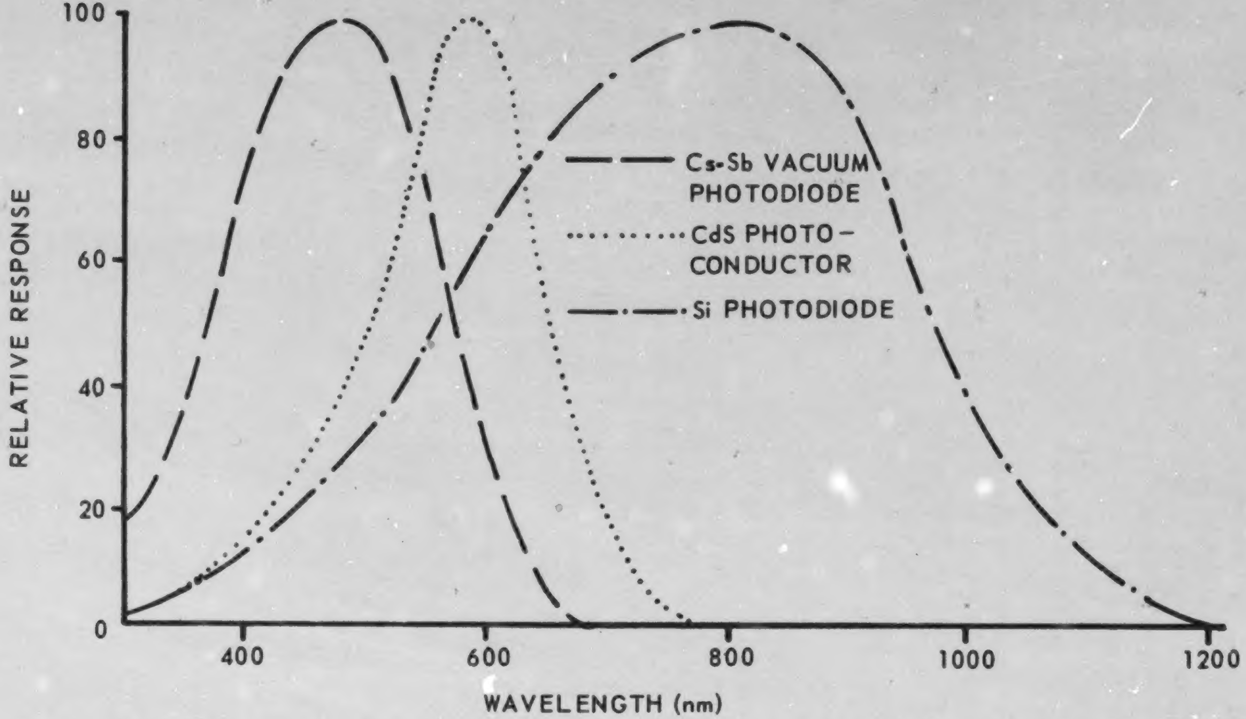


FIGURE 3. Relative spectral response of the three basic types of detector; a semiconductor photodiode, a photoemissive photodiode, and a CdS photoconductor. The relative response has been normalized to a peak of unity and the curves do not reflect the relative responsivities of these detectors.

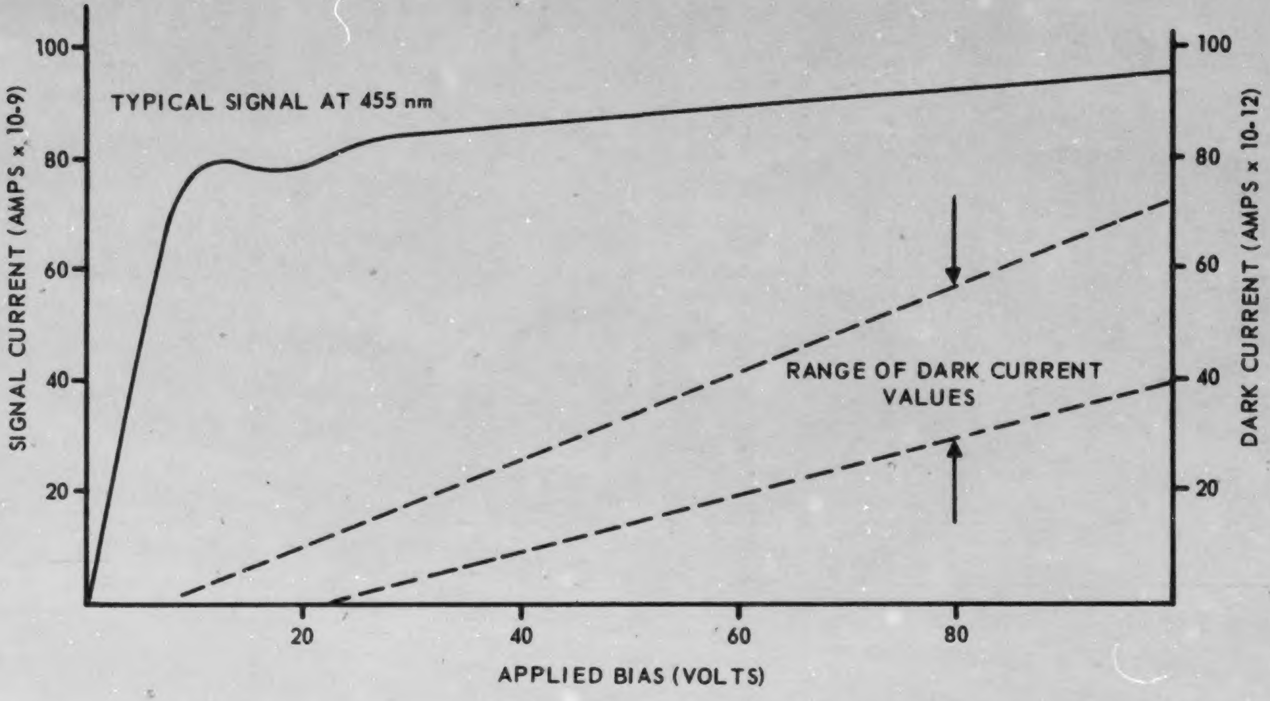


FIGURE 4. Sensitivity and dark current of a group of vacuum photodiodes, as a function of the applied bias potential.

at a low bias potential. Table 2 summarizes the results of testing the three major types of detectors available for radiometric monitoring instruments; photoemissive detectors such as the vacuum photodiode, photoconductive detectors represented by the cadmium sulfide cell, and photovoltaic and photodiode detectors represented by unbiased and back-biased silicon photodiodes, respectively. It seems clear that there are distinct advantages in this case to using a photoemissive detector, such as a vacuum photodiode or photomultiplier.

Upon achieving suitable measurements of dosage rate, however, it is still necessary to obtain the total dosage by multiplying the dose rate by the total duration of exposure. The potential for error in this process is of course high, since errors may be made in either the measurement of the duration of exposure or in the dosage rate since the irradiance impinging on the baby may vary with time due to either changing illumination or to changes in the position of the baby. Thus it may be desirable to measure the dosage directly, by some sort of actinometric measurement.

Actinometric measurements are among the oldest techniques in the measurement of light and are commonly used in the measurement of ionizing radiation. Both electronic[9] and chemical actinometers may be devised and should prove useful in monitoring phototherapeutic dosage; however, the comments regarding radiometric instruments apply equally to actinometric instruments, in that the spatial and spectral response functions must be chosen carefully if consistent results are to be obtained.

The advantages of actinometry over the simple radiometric measurement combined with a measurement of the exposure duration include (1) the ability to measure dosage accurately when using pulsed or intermittent illumination during phototherapy; (2) the ability to measure dosage during periods of changing illumination, such as that due to adjacent phototherapy lamp units or periodic exposure to sunlight; and (3) the fact that the measurement is made in one step and need not necessarily include a concurrent measurement of the duration of the exposure. In addition, actinometric measurements may be simpler and less expensive than their

TABLE 2. *Summary of characteristics of the four basic detector types*

Characteristic	Photoemissive	Photoconductive	Photovoltaic[1]	Photodiode
Sensitivity	10^{-10} W	10^{-8} W	10^{-10} W	10^{-7} W
Responsivity	0.025 A/W	0.1 A/W	0.3 A/W	0.3 A/W
Temp. sensitivity (per °C)	0.1%	0.6%	0.6%	0.2%
Dark current	10^{-12} A	10^{-10} A	—	10^{-7} A
Peak sensitivity	480 nm	580 nm	800 nm	800 nm
Linearity	4 decades	2 decades[2]	3 decades	4 decades

[1] No bias voltage.

[2] Temperature dependent.

Note.—W = watt, A = area, nm = nanometer.

radiometric counterparts, and may certainly be expected to consume less labor.

SUMMARY AND CONCLUSIONS

The practice of phototherapy for the treatment of hyperbilirubinemia has generated a need for instrumentation to measure dosage rate (irradiance) and total dosage (exposure) in the region effective in the photodecomposition of bilirubin in vivo. Existing instrumentation is generally inappropriate for a variety of reasons, including the fact that most radiometric instrumentation has been designed for use in the visible and near-infrared regions, whereas little attention has been paid to instrumentation for the far blue regions. Thus the potential user of phototherapy monitoring instrumentation must pay particular attention to the spectral response of the apparatus that he wishes to use. This becomes particularly important during calibration, since tungsten lamps are normally used as calibration sources and any residual red or infrared response in the detector will cause the meter to read too low a value after calibration, when used to monitor the output of fluorescent lamps.

An additional problem area involves the spatial response of the measuring instrumentation. If the system does not provide a uniform angular response or if the angular response affects the spectral response, as is frequently the case when using thin film filters, the relationship shown in equation 4 does not apply and erroneous results may occur.

The most important systematic error, however, is the lack of a suitable action spectrum for construction of a filter detector response function, that can be easily used by manufacturers. In the absence of such a standard action spectrum, comparison of results may be facilitated by using the absorption spectrum of bilirubin in chloroform as an interim standard. Should a standard in-vivo action spectrum become available at some future date, results could be converted easily from one standard to the other.

Finally, the need for two separate measurements, that is, both dosage and dosage rate, generates a need for suitable actinometric methods for measuring dosage directly. These methods may be either electronic or chemical, but in either case will perform the time integration of the irradiance automatically, thus permitting the accurate measurement of pulsed or intermittent illumination. Thus actinometric measurements will permit dose-response relationships to be established as a function of both peak irradiance and total dosage, during the process of pulsed phototherapy.

In summary, instrumentation suitable for the task of monitoring phototherapy at the clinical level is not readily available. The technical feasibility of constructing suitable instrumentation, however, has been established, and the design principles are straightforward. Thus it may be anticipated that such instruments will be available commercially in the near future. In the meantime, the researcher may obtain suitable accuracy by carefully choosing a radiometric instrument capable of making the measurements from among those that are available.

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Discussion

Dr. Brown: When you measure light at the wavelength apparently effective for altering bilirubin, are you really measuring the total irradiance that the baby receives from other sources?

Dr. Anderson: If you are simply looking at one wavelength interval, you are only looking at the irradiance in that wavelength interval. Of course, this can be converted to total irradiance if you know something about the spectral composition of the light that is impinging on the baby. If you really want to know how much irradiance is actually falling on him, you have to make a broadband measurement simultaneously, or if you are interested in irradiance in other bands, it is necessary to measure them independently.

Dr. Brown: Since the conference is devoted to long-term implications and since we do not know where some of the problems may lie, we do have to think about other areas of the spectrum that may be producing effects.

Dr. Indyk: I would like to clarify a few small points in my presentation and ask a question.

The first concerns the matter of the 200-hour delay of the blue bulbs reported some time ago. Those bulbs were prototypes and I am assured that the super blue bulbs now made have lifetimes on the order of *X* thousand hours without a visible change in the spectral output. Therefore, the bulbs that Dr. Ogawa presented, daylight cool white and super blue, last for a long time.

Second, is the matter of the reflector. It should be a polished or near-polished clean aluminum reflector, so that you can have a good reflection of blue.

Third, concerning the question of the site of action of light on bilirubin in the skin, Vogl, in his reported experiment defined borderline between bilirubinated and nonbilirubinated skin, within about 0.2 millimeter and calculated the depth of the bilirubin containing skin at about 0.2–0.4 millimeter. I looked at it by analyzing the absorbance of light and I also come up with around 0.2 to 0.4 millimeter of skin. We are both asking, Where is the bilirubin stored in this 0.2–0.4 millimeter layer?

Dr. Brown: Dr. Vogl, did you want to respond?

Dr. Vogl: I am curious as to where in the skin bilirubin is stored. Particularly, to what is it bound so tightly?

Dr. Zuelzer: One place that we know is in the endothelium in the blood vessels.

Dr. Schmid: You have pigment in the sclera.

Dr. Brown: We are talking about anybody's skin, preterm babies' skin, full-term babies' skin. Skin is variable in nature. It varies with gestational age.

Dr. Ostrow: The subcutaneous fat of the Gunn rat contains a large amount of bilirubin. In addition, bilirubin binds to elastin, which is cationic and could act as an anion exchanger.

Dr. Gartner: In the studies we have done with adult and newborn Rhesus monkeys, where we were infusing them with very large amounts of unconjugated bilirubin, achieving very high serum concentrations, we have measured the indirect and direct reacting bilirubin concentrations in a number of tissues. Unfortunately we did not study skin. Among the tissues studied (fat, muscle, lung, kidney), lung has the highest concentration of unconjugated bilirubin except for liver. With histological examination of lung after infusion, pigment is found primarily on the alveolar lining. There is some elastin in lung but there is a great quantity of phospholipid, particularly in the alveolar lining.

Dr. Brown: Perhaps Dr. Johnson could comment on the long-term observation that the full-term baby was more protected from the maldistribution of bilirubin than was the preterm baby, presumably in part because there was more subcutaneous tissue in which to store bilirubin. Further, we have observed that the preterm infant, at least in terms of decrement in bilirubin under phototherapy, does not respond quite as well as the full-term baby. Is this an indication that less of the bilirubin is in the skin, available to the action of a photon?

Dr. Johnson: In this connection, I would like to mention our work with the Gunn rat. The small, thin animal with a low rate of weight gain has a much higher incidence of fatal kernicterus or grossly evident kernicterus than his well-fed fat counterpart. We can, changing to a high-fat Purina breeder chow for the mother, significantly decrease brain damage in her suckling young. Similarly, jaundiced adult females fed standard Purina lab chow breed very poorly. Few pregnancies seem to occur and even fewer are carried to term. Those that are result, with rare exceptions, in puny small litters that do not survive and that the mother cannot adequately nurse. In contrast, breeder chow fed jaundiced females breed very well and rear healthy litters. Especially if the litter size is kept at eight or below, the severity of brain damage will be less than in the young of heterozygote mothers fed standard lab chow. The main difference between the two chows is in the fat content, which is 11 percent for the Purina breeder chow and only 4 percent for standard lab chow, and the main difference in the suckling young seems to be their degree of fatness.

Dr. McDonagh: We have a similar effect with green breeder chow. I might point out that the manufacturers told me that the only difference between the green breeder chow and the regular chow that we feed the rats is that the green breeder chow contains alfalfa and a fish-soluble fraction.

This is a fish, water-soluble fraction that is obtained from tuna canning factories.

Concerning the uptake and release of bilirubin by skin, there is a recent paper by Kapoor, Murti, and Bajpal (*Biochem J.*, 136:35–43, 1973) that reports the uptake of bilirubin from solution by skin segments of rat, mouse, and guinea pig.

I would like to ask Dr. Anderson a couple of questions. First, what is the stability of the bilirubin in those badges in the dark? What sort of lifetime studies have you done?

Dr. Anderson: I have had film badges in various polymer matrices for as long as several months and, so far, they seem to be reasonably stable over that period of time. I do not know about anything longer, but I am, of course, continuing to study that.

Dr. McDonagh: Is it possible that the stability might vary from city to city, depending on the pollution?

Dr. Anderson: I tried to avoid that by using a high molecular weight mylar to enclose the whole thing. That is done with a relatively inpervious cement to sandwich the layers together. I made them in a glove box, in a hydrogen atmosphere. So I do not think there is much permeability in the badge, from anything that is indigenous to the local air.

Dr. McDonagh: If you place the badge on the baby's diaper, will you get a different apparent value?

Dr. Anderson: I am looking into that right now. If that happens to be the case, I can easily make the back of the badge opaque or reflective. At this point, I consider this to be very developmental.

Dr. Odell: We have studied a child with Crigler-Najjar syndrome at 2 to 3 months of age. His physician reported to me that the bilirubin was climbing again despite phototherapy and agar treatment. We had two options. One, we could either switch to a blue lamp that had been reported more effective than the light bulb the physician was using, or use the special blue lamp of Westinghouse. The alternate was to put him on more agar. By putting him on more agar, his bilirubin was brought back down without changing the amount of phototherapy that he was getting..

When he was 12 months of age, we wondered if the agar was still working. We stopped the agar. (The boy had a bilirubin level between 12 and 14 milligrams percent for almost an entire year.) Within four days, his bilirubin was up to 21 milligrams percent and his family brought him in and said, "He is lethargic and not responding well." We had stool excretion data during the week before stopping agar, while he was off agar, and when agar was reinstituted. While on agar his pigment excretion was twice as great as when he was off agar.

We believe that the observations that Schmid and Lester made a number of years ago are relevant. If you have free bilirubin in the gut, then it can be reabsorbed, unless you can trap it.

Dr. Thaler has said that cholestyramine therapy in conjunction with phototherapy did much the same thing: It was preventing enterohepatic circulation of the bilirubin.

Dr. Brown: Earlier in this session, Dr. Schmid, you made a statement that disturbs me, because I think this concerns one of the points this conference might have some concensus on, what to do with this admixture of observations. They certainly do make one concentrate on the fact that after phototherapy there may be excretion of unconjugated bilirubin into the gut. Otherwise, these observations are really not explicable. You had said earlier today that somebody's observation destroyed the concept that the major effect was on the excretion of the unconjugated bilirubin.

Dr. Schmid: What I meant to say, Dr. Brown, was that the finding of Dr. Ostrow, that the cirrhotics excrete increased amounts of conjugated bilirubin, makes the light phenomenon less specific than we previously had assumed.

In Gunn rats with high unconjugated bilirubin, the question was, Is the enhancement of biliary excretion under light specific for unconjugated bilirubin? Now, Dr. Ostrow finds that in conjugated hyperbilirubinemia, the same thing happens. So, obviously, it is not that specific a process, since it does not matter whether it is bilirubin or conjugated bilirubin.

Dr. Brown: I think we should not make the mistake of stating that these excretion processes are an all-or-none phenomenon. The older literature states that bilirubin can only be excreted when it can be conjugated. I think it is a quantitative phenomenon, something like bromosulphalein (BSP). It is quite obvious BSP is excreted as a conjugate, but this does not mean that you cannot excrete unconjugated BSP, although at a rate that is usually very much less. Now perhaps 20 or 30 percent is excreted unconjugated, where normally it is 1 or 2 percent. It is just conjugated for better excretion. I think the same thing probably happens for bilirubin. It looks as though in the newborn period there is simply a significant excretion of unconjugated bilirubin. I can imagine that one can manipulate the system, perhaps by pharmacological means—for example, cholestyramine—and increase this fraction. One mechanism is to use light. I have no idea what the mechanism is for this. I think this idea is extremely worthwhile, however, because it means that there is the potential of increasing the liver's ability to excrete unconjugated bilirubin. When the excretion of unconjugated bilirubin is increased, a steady state is reached at one given point where the enterophepatic circulation has picked up as much as it can. At this point you have to add something that attracts bilirubin in the gut in order to prevent reabsorption in order to get another drop in serum levels.

With this perspective, I really think we ought to reexamine those clinical situations, particularly in the newborn, in which a lot of the success of phototherapy has been observed—notably in things like biliary atresia, or perhaps, high intestinal obstruction.

Dr. Ostrow: Callahan and Schmid (*Gastroenterology*, 57:134–137, 1969) showed that the output of unconjugated bilirubin in the bile of the Gunn rat increased moderately with infusion of bile salts, but increased strikingly with the infusion of conjugated bilirubin. This was presumed to be on the basis of complex formation. We do not know the mechanism, but it is an important mechanism.

Of course, the photoproducts themselves may have an enterohepatic circulation. Some of them, at least the ones I found in Gunn rat bile, are quite soluble in chloroform at pH 7.0. They may recirculate and their enterohepatic circulation might be interrupted by cholestyramine. This has not been looked into. Some of the so-called persistant bilirubinemia may actually be recirculation of a diazo-reactive derivative. I think this whole enterohepatic aspect needs clarification.

Dr. McDonagh: I do not think there is any question that the light causes unconjugated bilirubin to come out in the bile, and also in the urine. The question we do not know the answer to is the relative importance of these two processes. There is the bleaching effect and the unconjugated bilirubin effect. Now the studies on the Gunn rat seem to indicate that the major effect is the pushing out of unconjugated bilirubin. These studies, however, may be very misleading, because the rat was injected with labeled bilirubin and then allowed to sit for 12 hours before starting the experiment. We do not know whether 12 hours is long enough for the labeled bilirubin to mix with that in the skin, since the results that you get from that type of experiment may underestimate the amount of photooxidation products that occurs. I think it is very important to determine the proper ratio of these processes under light.

The second thing is that if we can potentiate the uptake of unconjugated bilirubin in the liver by light, it is possible that the effect may also be relevant to the uptake in the brain. If this latter occurred and if you do not use a binding agent to pull bilirubin out, phototherapy would be hazardous.

Dr. Brown: This is something some of us have been discussing. This danger becomes a possibility once you raise the specter of not having altered the bilirubin so that it cannot enter the brain. It is the assumption from the Diamond and Schmid paper (*Arch. Neurol.*, 18:699, 1968), that the photoaltered products of bilirubin are water soluble; it has been assumed, therefore, that one did not have the threat of kernicterus after such alteration.

Dr. Vogl: A suggestion was made regarding my data about which I would like to comment. I do not think my study says anything about preterm versus full-term infants. Just because the phototherapy acts in the first few layers of skin, at least in part, does not mean that this is where the majority of the bilirubin is necessarily stored. So I think the storage question and the decomposition question may be two different questions. I do not think we should confuse them.

Dr. Kapitulnik: One comment for Dr. Schmid, an observation about the green stools. We did not find very impressive amounts of biliverdin in the stools, I will say that Dr. Friederiszick's observation is correct. In the Crigler-Najjar syndrome, the urine is more orange than normal urine. We could not find any unconjugated bilirubin in the urine.

Dr. Brown: Dr. Alexander, did you want to make any comments about the questions that you think the National Institute of Child Health and Human Development study will answer?

Dr. Alexander: I think that we are going to have several advantages in doing this study that no other studies have had. First, we will have a randomized light-treatment, no-light-treatment sample of very large size, approximately 1,100 infants in each group, that should provide us with some answers on both immediate consequences of phototherapy and 1-year outcome of these infants. With the large size of this study, our statisticians tell us that we will be able to pick a twofold difference in incidence of any of the variables that we may be looking at, so that we should be able to detect anything that may have been missed in studies of smaller sample size.

Another thing that we will have available will be the instrumentation for measuring the dose of light received by the infants under phototherapy—for the first time, we will have good light dosage information. These infants will be available for correlation with studies of efficacy.

Dr. Schmid: I do not think anyone would doubt that if you have a baby, or for that matter, an adult or an adolescent, with a very high unconjugated bilirubin level, this individual is in danger of developing bilirubin toxicity because of the high bilirubin level itself. But if you got to lower bilirubin levels, down to 20, 15, or 12 milligrams percent as Dr. Johnson discussed yesterday, so many other factors enter into the picture—dehydration, acidosis, infection, medications, and so on—that I am sure you are going to get answers.

I would suggest that you may want to use the same mechanism that is now being used in the gall stone dissolution study. Chenodeoxycholic acid, obviously, dissolves gall stones, but there are many unanswered questions.

As for phototherapy, I think that ancillary studies should be developed directed toward answering the questions that have been discussed in the last 2 days, such as, Why is there reexcretion of the unconjugated bilirubin during phototherapy? What is the chemical reaction rate of the photodecomposition? I think that it would be a mistake to just move in the clinical direction and disregard the other aspects.

Dr. Zuelzer: I can only echo Dr. Schmid's view. The only purpose of the treatment of hyperbilirubinemia is to protect people from brain damage. I do not see that the question to be studied is directed at this central problem, because the vast majority of these babies, with or without exchange transfusions and with or without phototherapy, are not in jeopardy. We cannot know, from this study, which factors are critical in the development of kernicterus.

Dr. Lucey: I do not think the final answers are going to come out of the study for the same reasons that have been expressed. In addition, I think we continue to oversimplify the idea of followup. We all agree that light causes a number of things and we all agree that bilirubin is important, but in the lifespan of an individual the light exposure that an infant gets during the first few days of life is infinitesimal compared to his total natural light exposure, plus a number of other variables that are uncontrollable. In 1 year of time, it will not be possible to get a full answer.

Dr. Brown: We recognize the limits of this or any similar study today for obviously every effort must and will be made to prevent brain damage in the groups under study. In the study, we should be able to determine whether phototherapy is as effective, or more effective, than exchange transfusions in preventing kernicterus. Further, we should gain understanding of the factors critical to development of brain damage if any should occur since, for the first time in a large study population, factors known to predispose to kernicterus will be monitored prospectively. In addition, we are searching for any hitherto unsuspected side effects and long-term sequelae of light therapy itself. We may, from the study, also learn whether prevention of significant bilirubinemia in the very small infant improves the potential mental capacity, since we do not know today what level of bilirubin is without damaging effect on the brain.

We all agree that a 1-year followup is a very limited one, but that is a budgetary constraint, not a conceptual one. The investigators involved are very aware of the need for longer followup of such a study population and hope that funds will become available for such followup.

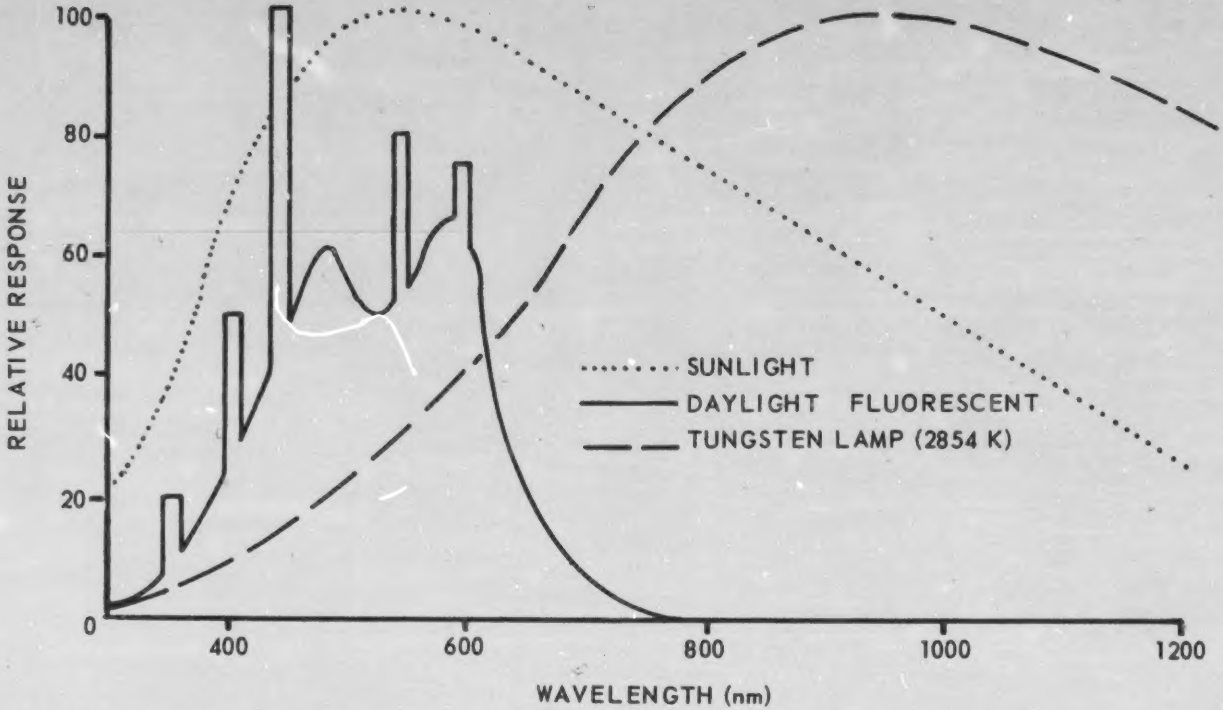

FIGURE 2. Relative spectral output of various light sources, including the sun, a typical fluorescent lamp, and a tungsten lamp. The spectra are normalized to a peak amplitude of unity and do not reflect the relative radiance of the sources.

Conclusions and Directions for the Future

Dr. Schmid: As I look over this conference, I get the impression that in some areas we really are about at the same place as we were 3 or 4 years ago. We really do not have more answers than we had then.

In a couple of other areas, on the other hand, we have made progress. It seems to me that we have at least some preliminary indication that light, in a dose given for phototherapy, over the short period of time of the treatment, given a few days or a week, at least from preliminary indication, probably does not have major deleterious effects. I realize that these infants have to be followed up over longer periods of time, but at least so far, over the period of observation, I feel a little bit more encouraged, since it looks like we are not causing any detectable harm.

I think the other area where we have made progress is in beginning to understand what happens in the breakdown of the bilirubin—the discovery that light increases the excretion of unconjugated bilirubin.

Dr. Brown: The information presented here these past few days represents the present state of information concerning long-term effects of phototherapy used in the treatment and prevention of hyperbilirubinemia. The aggregate of information has not revealed any uniform, significant, or lasting detrimental effect other than the temporary delay in growth of premature (but not small-for-dates) infants described by Dr. Ploussard. Most participants agree, however, that only a few of the long-term studies were prospective and, therefore, few were set up with controls for specific guidelines for introduction of light, or with detailed long-term study of sequelae.

The questions raised at this meeting should form the focal point for continued investigation of the "pharmaceutical photon." These questions direct our attention not only to the action of the photon on the bilirubin molecule, but on the physiology of the infant as a whole, as well as on the other substances, exogenous or endogenous, in circulation, or in the tissue, that must simultaneously be exposed to the action of this agent.

Further, we leave this conference emphasizing what we realized over 14 years ago, that while bilirubin is the sine qua non of the development of kernicterus, kernicterus obviously has a multiplicity of other contributing causes. Identification of the infant at risk is still difficult, and obviously better criteria for selection must be developed so that therapy is directed only at infants at risk. Only in this way will any potential danger from a therapeutic agent be minimized and in a sense justified. Further, any therapeutic or preventive agent for hyperbilirubinemia must be shown to prevent kernicterus. Dr. Schmid has emphasized that much more work is needed concerning the means by which phototherapy leads to excretion of unconjugated bilirubin. We all agree that basic as well as clinical studies concerning the mode of action as well as the safety and efficacy of light therapy are still very much needed and that the study recently undertaken by the National Institutes of Health should be supported.

We thank you very much for being with us.

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